REVIEW

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An Updated Review of Exocrine Pancreatic Insufficiency Prevalence finds EPI to be More Common in General Population than Rates of Co-Conditions

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ABSTRACT

Exocrine pancreatic insufficiency (EPI) is frequently described as underscreened, underdiagnosed, and undertreated. The treatment for EPI is pancreatic enzyme replacement therapy (PERT), which is costly, and provider confidence in prescribing may be one barrier to reducing undertreatment. The lack of interchangeability studies for prescription PERT and/or lack of efficacy studies of over-the-counter enzyme options may be another barrier. This paper reviewed the prevalence of EPI in the general population and in co-conditions. Prevalence of EPI in the general population is commonly estimated around 10-20%, and further research is needed to evaluate EPI across all age groups and to better understand in which age group EPI becomes more prevalent, as an age effect is often seen in EPI prevalence studies. EPI is perceived to be highly correlated with certain co-conditions, and the majority (~65%) of EPI literature is related to a co-condition such as cystic fibrosis, pancreatitis, post-surgery, cancer, or diabetes. It can be estimated that 85% of literature in identified co-conditions, or 56% of total EPI literature, is on rarer co-conditions which only represent <1% of EPI overall. In contrast, there is very little research and literature on EPI in the general population. The highest absolute rates of EPI with co-conditions are likely diabetes and possibly irritable bowel syndrome with diarrhea, yet they are among the least commonly researched in co-condition and EPI studies. A lack of research on EPI in the general population and in the more common co-conditions may be contributing to the rates of underdiagnosis and underscreening, as well as undertreatment for those with low fecal elastase-1 levels.

Key words: exocrine pancreatic insufficiency – EPI – PEI – pancreatic enzyme replacement therapy – PERT – prevalence – cost.

Abbreviations: EPI: exocrine pancreatic insufficiency; FE-1: fecal elastase-1; IBS: irritable bowel syndrome; IBS-D: IBS diarrhea type; PERT: pancreatic enzyme replacement therapy.

INTRODUCTION

Exocrine pancreatic insufficiency (EPI or PEI) occurs when the pancreas no longer makes enough enzymes to help the body digest food on its own, which can be treated with pancreatic enzyme replacement therapy (PERT) [1]. Previous literature suggests that EPI is underdiagnosed, underscreened, and undertreated [2-5].

This article studied the EPI-related literature, particularly evaluating evidence related to underdiagnosis, undertreatment, cost of associated therapy, and general population prevalence of EPI.

A literature review was conducted, in Google Scholar for the search string: „Exocrine Pancreatic Insufficiency" OR „Pancreatic Exocrine Insufficiency" OR „Pancreatic Insufficiency" OR „Pancreatic Enzyme Replacement Therapy". The search strategy was to identify EPI-specific articles (including EPI treatment with PERT). Titles were manually screened and categorized based on topic (animal, if it was an animal study; by co-condition if it was cystic fibrosis, diabetes, pancreatitis, surgery, cancer, or other; and otherwise, if it was treatment or diagnosis in general). Animal-related studies were then filtered out, leaving 649 articles (Fig. 1). Another content sub-analysis was done to review content of articles assessing prevalence in the general population and screening recommendations.

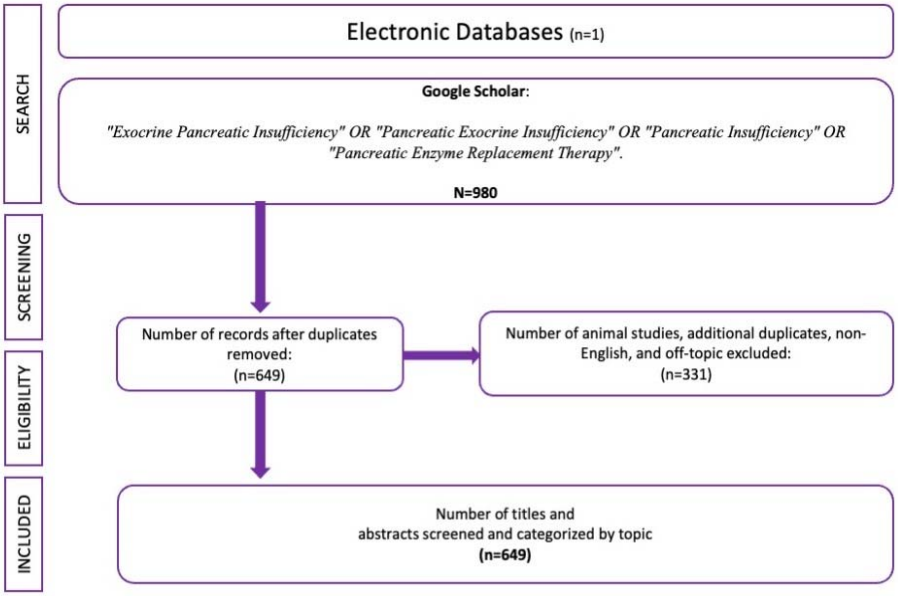

Fig. 1. PRISMA diagram illustrating search strategy, article categorization and review.

EPI IS UNDERDIAGNOSED

Exocrine pancreatic insufficiency is diagnosed based on a combination of symptoms; possible indicators of malnutrition; and a non-invasive stool test [1]. The clinical manifestations can be nonspecific, which may lead to the lack of timely recognition and diagnosis [6], and quality of life impacts can be significant [7]. The historical gold standard test for EPI has been a 72-hour fecal fat quantification test but is disliked by patients and laboratories; instead, fecal elastase-1 (FE-1) is a reliable, non-invasive and less time-consuming test [8]. For patients with known risk factors such as highly correlated co-conditions, the non-invasive tests are sufficient for diagnosis [9]. EPI is correlated with chronic and acute pancreatitis, pancreas surgery, cystic fibrosis, type 1 and type 2 diabetes, older age, advanced renal disease, Sjögren's disease, celiac, IBS-D, IBD, HIV, alcohol-related liver disease, and use of somatostatin analogues among others [10, 11].

A 2019 study used machine learning and found that the number of patients likely to have EPI was about 12 times the number of patients directly identified as EPI-positive through a claims analysis in the study population (age <64) [12].

Developing additional non-invasive tests or screening for EPI is usually highlighted as an ongoing research need, particularly since symptoms of EPI are often non-specific [13].

EPI IS UNDERTREATED

As early as 1959, it was apparent that the timing and quantity (dose size) of pancreatic enzyme replacement therapy (PERT) matters for the treatment of EPI [14]. In 2005, the timing schedule between before, during, and after meal dosing of PERT was evaluated, assessing that enzymes distributed throughout or immediately following meals resulted in 7.5% and 6.6% improvements in fat digestion respectively [15]. A 2014 study subsequently found a mismatch between the timing of the emptying of the meal and the enzyme activity, suggesting that timing optimization, such as mixed dosing before and during a meal, may be beneficial alongside dose sizing optimization for improving therapy outcomes. A 2021 systematic review concluded the sphere size in approved, enteric-coated PERT is not essential for dose efficacy, but rather the lipase content (dose sizing) and acid protection [16].

Petersen et al. [16] report that the needs of people with EPI vary based on factors including meal composition. Dose sizing, timing, acid protection, or individual meal composition may cause unsuccessful outcomes with the initial PER prescription, and titration is often needed. Clinicians may not be initiating PERT treatment for patients whose FE-1 levels and symptoms meet diagnostic criteria. When PERT is prescribed, prescriptions are often not updated to titrate enzymes. Shandro et al. [17] recommend against restricting dietary fat intake, and instead individualizing PERT dosing according to size and fat content of each meal rather than prescribing a fixed dose regimen. Only one randomized trial has compared the efficacy of a fixed dose regimen versus the typical real-world practice of individualized self-titration [18], concluding efficacy is higher when enzymes are self-dosed by patients in a flexible manner [19].

Variability has always been high between enzyme production runs, from 1975 [20] until a 2004 review by the FDA found inconsistencies that could "significantly compromise the safety and effectiveness" [21]. Pancreatic enzyme replacement therapy requires FDA approval since 2010: as of 2012 in the US there are 6 brands of FDA-approved PERT [22]. The clinical studies for approval did not evaluate comparative efficacy, so therapeutic interchangeability between approved products is unclear [23]. Studies in Europe in 2009 [24] have also found variation between brands, and in Russia as recently as 2020 [25] variation was found within different production runs or batches within an in vitro study evaluating lipase activity.

Variation and inability to accurately rely on dose quantities reported on the label is one of the criticisms of over-the-counter formulations of "digestive enzymes" that are frequently used

by people with EPI and/or other digestive complaints, for which clinical trials and formulation research are lacking [26]. Ironically, similar variability exists in production runs with approved PERT products. Research is needed evaluating activity, variability, and efficacy of both common over-the-counter and prescription enzymes in people with EPI.

Systematic reviews evaluating evidence for treatment of EPI [9, 27] are usually for co-conditions such as cystic fibrosis [28] or pancreatitis [29, 30], and usually do not consider titration or timing when reviewing efficacy of PERT. Most report improvements in fat absorption, quality of life, and symptom reduction following PERT [31]. A 2017 meta-analysis evaluated efficacy and safety of PERT in adults with EPI regardless of related etiology from 7 RCTs with 282 patients and confirmed PERT is safe, effective, and tolerable in people with EPI regardless of co-condition [32].

In many cases, treatment inadequacy can be due to inadequate prescription, mismatched dose timing, or inability to afford PERT [33]. Many providers are still uncertain about the indications for prescribing and effective dosage [34]. Variabilities within brands may cause people with EPI to struggle; providers should suggest switching to an alternative if symptoms do not resolve once titration and timing is addressed [35]. A 2021 study found that a third of people with EPI surveyed (n=75) perceived gaps in patient-physician dialogue regarding PERT [36]. Future research should address healthcare provider awareness barriers to exploring different PERT options for people with EPI, support increasing provider confidence [37] in individualizing and titrating PERT prescriptions and educate providers [38] regarding meal-based PERT titration [19].

TREATMENT COSTS

Cost may play a role in PERT prescribing and treatment patterns. A 2012 economic analysis of PERT costs for those with EPI (related to chronic pancreatitis) in Poland found PERT to be cost effective for the health system [39]. Because this study solely looked at PERT costs, it may also be applicable to people with EPI without chronic pancreatitis. In 2021, Gupta et al. [40] found total 30-day costs for PERT under Medicare Part D ranged from $2,109-$4,840, with out-of-pocket costs starting around $1,000 ($853-$1536) for deductible and coinsurance, another $673 ($527-$120) until people met "catastrophic coverage", and $135 ($105-$242) after reaching catastrophic coverage. Gardner et al. [23] showed PERT prescription costs had risen from $259 in 2008 to $582 in 2012. This rise in cost comes absent any research studies on interchangeability of PERT products [41], another gap in EPI-related research.

A non-peer-reviewed analysis in 2022 evaluated prescription PERT cost and found a per-pill price of $9 (~$0.36 per 1000 units of lipase), and that over-the-counter enzymes can be as low as $0.08 per 1000 units of lipase, but noted that quality and consistency may vary [42]. Another non-peer-reviewed analysis in 2022 estimated yearly cost of PERT in the US could range from $18,000 (6 pills daily, $8.34/pill) to $24,000 (8 pills daily, $8.34/pill) if one were to be uninsured; actual price will vary for those with insurance coverage, but a year's worth of PERT alone is likely to reach the deductible or out-of-pocket max cost of many employer-provided health insurance plans in the US [43]. The yearly cost of PERT has increased compared to Trang et al.'s [44] 2014 per-pill cost estimates, which extrapolate to ~$12,000-$17,000 per year.

In 2015, a study found no statistically significant difference in annual cost of PERT ($6881,63 ± 2334,04) in those with EPI with and without pancreatitis following a pancreatectomy [45]. Despite the high cost of PERT, studies of EPI in patients following surgery show that using PERT lowers total costs. A study in 2018 of 819 people with pancreatic cancer who received PERT following surgery suggested that overall healthcare resource use, medical costs, and total costs were lower in those who received PERT [46].

Providers should be aware of the burden of costs of approved PERT products for people with EPI, especially in those already burdened with the high costs of treatments for other co-conditions [43, 47, 48].

PREVALENCE RATES

The literature review search, after excluding animals, resulted in 649 articles then categorized by topics of: cystic fibrosis, pancreatitis, diabetes, cancer, celiac disease, surgery, and other, based on the most common and frequently associated co-conditions previously observed in the literature.

Overall, of studies whose study population could be identified through title and abstract review: 365 were EPI studies in rare co-conditions (117 cystic fibrosis, 79 acute and chronic pancreatitis, 66 other rare co-conditions, 61 surgery, 42 pancreatic cancer). In contrast, 58 were EPI studies in more common co-conditions (45 diabetes all types, 13 celiac disease, and 5 were found which specifically study the prevalence of EPI in the general population. Out of those 428 (365 rare, 58 not rare, and 5 general population) population-identifiable studies, that is therefore 85% (365/428) of EPI research in the more rare co-conditions (cystic fibrosis, pancreatitis, other rare co-conditions, surgery, cancer), whereas 14% (58/428) are in the more common co-conditions (diabetes, celiac), and 1% (5/428) studying the general. Out of the total of all studies, including those on treatment or diagnosis (n=649 total), 56% were therefore on EPI in rare co-conditions (365/649), 9% in EPI with the common co-conditions (58/649), while 21% were of general EPI treatment articles (135/649), and 14% were on general EPI diagnosis (91/649). It can be estimated that 85% of literature in identified co-conditions, or 56% of total EPI literature, is on rarer co-conditions which only represent <1% of EPI overall.

There are many estimates of the prevalence of EPI in related co-conditions. For example, Capurso et al. [49] 2019 review summarized prevalence estimates of 30-90% in chronic pancreatitis, 15-20% in mild acute pancreatitis versus 30-40% in severe acute pancreatitis, 30-60% in autoimmune pancreatitis, 20-60% in unresectable pancreatic cancer, 80-90% after pancreatic duodenectomy, 20-50% after distal pancreatectomy; 30-60% in benign pancreatic tumors before surgery, 80-90% in cystic fibrosis, 80-90% in Shwachman-Diamond syndrome, 20-30% in type 2 diabetes mellitus and 30-50% in type 1 diabetes mellitus, 4% in Crohn's disease and 10% in ulcerative colitis (collectively inflammatory bowel disease or IBD), 5-80% in

celiac disease, 10% in pediatric intestinal transplantation, 10-50% in HIV, 16% following esophagectomy, 40-80% after total/subtotal gastrectomy, 10-30% in Sjogren's disease, 15-30% in people age > 80 years, 10-20% in tobacco users and 20% in patients receiving somatostatin analog therapy.

Capurso et al. [49] and many others suggest that the prevalence of EPI in the general population is unknown. Yet, there is research that has assessed prevalence in the general population, as described below and summarized in Table I.

Campbell et al. [50] performed a multicenter retrospective analysis of all gastroenterology patients tested for FE-1 between 2009–2013 and found that of 1,821 patients, 13.1% had low FE-1 (<200μg/g), concluding that EPI is common in gastroenterology practice and that clinicians should have a low threshold for checking FE-1 in patients presenting with symptoms other than diarrhea. In this study patients with existing pancreatic diagnoses such as pancreatitis or cancer were excluded from the study, aligning this population more closely with the general population. Campbell also encourages testing of patients presenting with a variety of gastrointestinal symptoms to avoid missing diagnoses and potentially labeling patients with functional gut disorders [51]. Similar work found 15.4% prevalence even in primary care, which is similar to the above rates found in secondary care [52].

An earlier 2004 study assessed 914 participants aged 50-75 years old (mean age 61.9) from the general population and found 11.5% (n=105) had low FE-1 (<200μg/g) and 47 (5.1%) had levels <100μg/g [53].

A 2011 study evaluated 159 people aged 60-92 in Poland and Finland, without any special diet, known gastrointestinal disease, surgery, or diabetes mellitus; 53 young subjects (20-28 years old) were investigated as controls [54]. They reported the FE-1 concentrations were below the cut off level of 200 μg/g in 23 of 106 (21.7%) individuals [mean 112 (86-138) μg/g] and 9 individuals were below <100μg/g [54]. They concluded one fifth of healthy older individuals without any gastrointestinal disorder, surgery or diabetes mellitus have pancreatic exocrine insufficiency [54].

Collectively, these prevalence studies in the general population in both primary and secondary care suggest prevalence of EPI in the range of 11-21% of people without co-conditions (such as pancreatitis, other gastrointestinal disorders, or diabetes). A 2000 study found 19 of 105 individuals (18%, mean age 58 years, range 22-80 years) in a control group (as compared to an n=114 group of people with diabetes, where rates was 66%) had rates of low FE-1 <200 μg/g, further supporting this estimate [55].

Table I. Overview of exocrine pancreatic insufficiency prevalence studies in the general population

Author	Year	Study details	Population size	Prevalence (%)	Notes
Campbell et al. [50]	2016	Retrospective analysis evaluating FE-1 between 2009 and 2013 in GI clinic, excluding those with chronic pancreatitis, pancreatic malignancy or previously diagnosed EPI	1,821 tested in two gastrointestinal clinics, age 16-93.	13.1	Suggests GI practices and clinicians should have a low threshold for checking FE-1 for people presenting with symptoms other than diarrhea.
Campbell et al. [52]	2015	Retrospective analysis evaluating FE-1 between 2009 and 2013 in primary care clinics, excluding FE-1 tests from secondary care	168 primary care patients, mean age 59.74	20.2	Common indications to test were diarrhea (60%), weight loss (14.9%) and abdominal pain (13.1%). Of the 34 with low FE-1, 76.5% (26/34) had documented PERT, of which 80.7% (21/26) reported symptom improvement; 7.7% reported no benefit and 11.5% were unable to tell.
		Also evaluated secondary care patients	1,887 secondary care patients, mean age 51.60	14.4	
Rothenbacher et al. [53]	2004	Evaluate FE-1 in general population 50-75 years (mean 61.9)	914	11.5	Found increase with age. Suggested smoking as an independent risk factor.
Herzig et al. [54]	2011	Evaluate FE-1 levels in adults > 60 years in Finland and Poland without any special diet, known gastrointestinal disease, surgery, or diabetes mellitus	106	21.7	Found FE-1 correlates negatively with age. 53 persons were young (20-28 years) (controls) Did not report prevalence in control group or data; visual inspection suggests only one of the n=53 controls had FE-1 <200.
Hardt et al. [55]	2000	Evaluating FE-1 in control group (22-80 years, mean age 58), without diabetes, n=105, as compared to people with diabetes (n=114)	105	18%	This study compared a control group to people with diabetes; there was an even higher (66% of n=114) prevalence rate in the population of people with diabetes. The difference between the control group (prevalence 18%) and diabetes group was statistically different for both type 1 and type 2 diabetes sub-groups. This study, in contrast to others, did not see significant influence by alcohol consumption in either group.

EPI: exocrine pancreatic insufficiency; FE-1: fecal elastase-1; PERT: pancreatic enzyme replacement therapy.

Additional studies should be done in the general population in all age brackets; and in the meantime; gastroenterologists should be aware of these data and screen patients with gastrointestinal symptoms for FE-1.

A relatively high prevalence of EPI in subpopulations with co-conditions was observed, but contrasts with the likelihood of far higher absolute prevalence of EPI in the general population, as the only co-conditions listed above with >1% prevalence and elevated incidence of EPI in the general population are diabetes (10.5%) [56], and possibly celiac (1.4%) [57], whereas the others (Table II) are far less common (<1% prevalence) than EPI itself in the general population.

Table II. General population prevalence of commonly researched populations with exocrine pancreatic insufficiency

EPI Co-Condition	Estimated General Population Prevalence
Diabetes	10.5% [56]
Celiac	1.4% [57]
Cystic Fibrosis	0.04% [58]
Pancreatitis	0.04% [59]
Pancreatic Cancer	0.005% [60]

EPI: exocrine pancreatic insufficiency.

The initial review categorization did not highlight many articles on EPI and irritable bowel syndrome (IBS); the few articles fell into the "Other" category. However, IBS has an estimated 7.6-10.8% world prevalence [61]. Irritable bowel syndrome diarrhea type has a relatively high (second highest following diabetes, as seen in Table II) general population prevalence compared to the more-studied co-conditions of EPI described previously. A 2022 study found 5% of people with IBS-D also had EPI [62], which supports a 6.1% estimate from a 2010 study [63].

Although prevalence of EPI detected in this group may be relatively lower (~6%) compared to other co-conditions, the absolute prevalence estimated in the general population of IBS-D with EPI (0.04%) is likely to be higher than in any other co-conditions except diabetes and celiac. Even using the low end of the 7.6-10.8% general population prevalence rate of IBS-D times the low end of the 5-6% relative prevalence of EPI in IBS-D gives 0.04%, matching the overall prevalence in the general population of cystic fibrosis and pancreatitis, and far exceeding the overall prevalence of pancreatic cancer.

The overall population prevalence of cystic fibrosis, pancreatitis, cancer, and pancreatic-related surgery combined totals <0.1%, and the lower end of the estimated overall population prevalence of EPI is approximately 10%, which suggests less than 1% of the overall incidence of EPI occurs in such rare co-conditions.

We can therefore conclude that 99% of EPI occurs in those without a rare co-condition. In this analysis, we observe that little research on EPI occurs in those 99% of people with EPI (many of whom are undiagnosed). Specifically, we conclude that 56% of the total EPI research, and likely over 85% of research in easily identifiable populations, occurs in the relatively rare co-conditions (cystic fibrosis, pancreatitis, surgery, or cancer) that represent less than 1% of the overall population prevalence of EPI.

This suggests that there is more research that needs to be done in the general population and on EPI more broadly, without limiting the studies and findings to the rarer co-conditions which make up a minute fraction of EPI prevalence overall.

EPI SCREENING IN THE FUTURE

Prevalence of EPI is likely higher than many gastroenterologists might suspect, even among the general population. There are clear associations with co-conditions such as diabetes, pancreatitis, and other conditions, but there is also evidence of high rates of EPI prevalence in the general population, which further increase with age. The rate of EPI is even higher than most of the associated co-conditions.

The biggest knowledge gap in the surveyed literature is the estimated prevalence in the general population younger than 50 years old without associated co-conditions. That shouldn't limit screening in symptomatic individuals; however, as undiagnosed EPI is associated with substantial morbidity [64]. Additional research gaps highlighted in this article are summarized in Table III. Multiple studies [51, 65] have shown 80% of people with low FE-1 respond clinically and quickly

Table III. Summary of knowledge gaps in current EPI literature

- Pancreatic enzyme replacement therapy titration guidelines usually vary by associated co-condition; it remains to be studied whether general guidelines for people with EPI, regardless of co-condition, might be more useful. It is often unclear what evidence was used to determine different co-condition specific guidelines for PERT dosing in EPI, making it difficult to evaluate whether differences between guidelines reflect actual differences in medication requirements.
- Early 2010 era data suggests that even following the move to require regulatory approval for PERT products (in the US as an example), ongoing challenges with quality and consistency among brand production runs may be a factor in PERT efficacy. More research evaluating consistency is warranted, and updated guidelines to aid patients in accounting for inconsistencies is needed, including studies on use of over-the-counter options, which have a tradeoff between possible lower cost but higher pill burden and variation in reliability.
- There is an estimated general population prevalence of EPI of 10-20%. However, most research is on rare co-conditions (such as cystic fibrosis and pancreatitis) that represent <1% of EPI overall. More research on EPI is needed without limiting it to co-conditions. This would magnify the impact of research as it would then be applicable to >99% of the EPI population.
- There is a lack of research on age groups younger than 50 years of age in terms of general population prevalence.
- Even when diagnosed, evidence suggests EPI is frequently undertreated. However, studies show that >80% of people with low FE-1 show symptom improvement or resolution with PERT. Clinicians should be willing to suggest PERT treatment for a trial period for individuals who have symptoms and have FE-1 <200 and evaluate response after adjusting titration and timing strategies.

For abbreviations see Table I

to PERT, and the other 20% may also respond positively with additional dose adjustments, as people often need to titrate their dosing after the initial prescription. Repeat FE-1 testing can also be performed if there is diagnostic doubt, or PERT can be commenced to confirm symptom resolution in lieu of repeat FE-1 screening or while waiting for the second FE-1 screening. Pancreatic enzyme replacement therapy can be used leading up to the FE-1 screening (because fecal elastase is solely produced endogenously and is not present in PERT formulations), which is one of the benefits of using FE-1 rather than the historical 72-hour fecal fat test for assessing exocrine pancreatic insufficiency [66].

CONCLUSIONS

Most EPI literature is in co-conditions such as cystic fibrosis and pancreatitis, and knowledge gaps exist regarding prevalence rates in the general population across all ages. The prevalence of EPI in the general population is under-recognized by gastroenterologists and other healthcare providers and may be as high as 10-20%, which may influence underscreening and underdiagnosis of EPI. Research on EPI is mismatched: 56-85% of research focuses on populations likely making up <1% of the total estimated EPI population. EPI is likely of higher estimated prevalence in the general population than most co-conditions studied in conjunction with EPI, except possibly diabetes. Gastroenterologists should increase screening of fecal elastase in patients with abdominal pain or steatorrhea. Further research on EPI in the general population and improving screening, diagnosis, and treatment is needed.

Supplementary material: To access the supplementary material visit the online version of the *J Gastrointestin Liver Dis* at http://dx.doi.org/10.15403/jgld-5005

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