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Evaluation and Management of Exocrine Pancreatic Insufficiency (EPI): Pearls and Pitfalls

Mitchell L Ramsey, MD[1], **Phil A Hart, MD**[1], **Christopher E Forsmark, MD**[2]

[1]Division of Gastroenterology, Hepatology, and Nutrition, The Ohio State University Wexner Medical Center, Columbus, Ohio, USA

[2]Division of Gastroenterology, Hepatology, and Nutrition, University of Florida, Gainesville, Florida, USA

Abstract

Purpose of Review: The diagnosis and management of exocrine pancreatic dysfunction (EPD) can be challenging. EPD classically results from conditions which cause loss of pancreatic acinar cell function and decreased digestive enzyme production. However, several conditions may contribute to signs or symptoms of EPD with otherwise normal pancreatic exocrine function. A thoughtful approach to considering these conditions along with their specific therapies can guide a tailored management approach.

Recent Findings: An EPD severity classification schema has been proposed, which emphasizes a shift towards more restrictive prescription of pancreas enzyme replacement therapy (PERT) for patients with milder EPD. In contrast, PERT use has been associated with a measurable survival benefit among individuals with EPD and pancreatic cancer, so prescription of PERT may be more liberal in this population. Recent publications in the cystic fibrosis (CF) population offer pearls guiding the titration and optimization of PERT.

Summary:

Among individuals with severe EPD, PERT is an effective therapy. Among individuals with milder EPD, although PERT is effective, there may be opportunities to provide additional and potentially more effective therapies.

Keywords

Cystic fibrosis; exocrine pancreatic insufficiency; exocrine pancreatic dysfunction; steatorrhea

INTRODUCTION

Exocrine pancreatic dysfunction (EPD) should be considered in a variety of clinical scenarios. It is usually considered on the differential diagnosis for chronic diarrhea (especially steatorrhea), fat soluble vitamin deficiency, and post-prandial digestive

Author of Correspondence: Mitchell L Ramsey, MD, 395 W 12th Ave, 2nd Floor Faculty Office Tower, Columbus, Ohio 43210, Telephone: (614) 293-6255, Mitchell.Ramsey@osumc.edu.

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symptoms such as bloating or flatulence. However, non-specific symptoms and uncertainties with interpreting pancreas function tests can present challenges to making a confident diagnosis of EPD. In addition, screening for EPD may be indicated among at-risk populations, including patients with pancreatic tumors or chronic pancreatitis (CP), or individuals recovering from an episode of acute pancreatitis (AP). Treatment of confirmed EPD involves exogenous pancreas enzyme replacement therapy (PERT) titrated to eradicate symptoms, normalize fat-soluble vitamin levels, and improve overall nutritional status. Patients diagnosed with severe EPD should be monitored for downstream nutritional consequences of fat malabsorption.

The purpose of this review is to highlight recent publications related to EPD that can guide clinicians to form a broad management strategy for this challenging clinical scenario. Non-pancreatic causes of fat malabsorption (such as post-bariatric surgery and other causes of postcibal asynchrony) will be examined as part of the differential diagnosis, but the management of these conditions is beyond the scope of this review. We will discuss several management pearls and will present supporting data from recent publications when available. Lastly, we will discuss common pitfalls in the management of EPD and will suggest measures to avoid these missteps.

DIAGNOSIS

Steatorrhea – the hallmark symptom of exocrine pancreatic insufficiency (EPI) – does not manifest clinically until over 90% of the enzyme producing capacity of the pancreas is lost.[1] However, EPD exists on a spectrum, where milder reductions in pancreatic enzyme production may lead to less severe manifestations, such as bloating and flatulence, but without overt steatorrhea. It is clinically meaningful to distinguish EPI from milder EPD since the differential diagnoses and management strategies differ between these diseases.

A recent review by Khan, et. al., provides a detailed algorithm for staging the degree of EPD, using fecal elastase (FE-1) and/or coefficient of fat absorption (CFA), clinical symptoms, and fat-soluble vitamin levels to determine the EPD stage (Table 1).[2] The authors propose reserving the label EPI for subjects with FE-1 values <100mcg/g and/or CFA <85% and clinical symptoms. Among individuals diagnosed with EPI, many will have a known pancreatic disorder likely to cause EPI (e.g., CP), and those without a history of pancreatitis may benefit from genetics evaluation for hereditary syndromes associated with EPI.[3–6] This investigation may reveal insights into screening for related conditions, such as more frequent screening for diabetes among individuals with pathogenic variants in the carboxy ester lipase gene (*CEL*).[7] In contrast, individuals with FE-1 ≥100 and/or CFA ≥93% without fat soluble vitamin deficiencies do not require PERT, but instead should be investigated for alternate causes of presenting symptoms, such as celiac disease (Table 2). Indeed, subjects with suspected EPD are a heterogeneous group and non-pancreatic etiologies must be considered prior to embarking on lifelong treatment of PERT, which can be cumbersome and costly.[8]

The prevalence of EPI is high among individuals with exocrine pancreatic disorders, including cystic fibrosis (85–90%),[9] CP (approximately 80%),[10] pancreatic cancer (approximately 70%),[11] and prior AP (approximately 25–40%).[12] The development of EPI

in these populations may be insidious, so objective laboratory assessment is warranted for screening at regular intervals.[13] Among asymptomatic individuals, checking annual fat-soluble vitamin levels is recommended, and this provides an opportunity to screen for severe EPI.[14] Additionally, annual serum trypsinogen levels might be considered, as this provides an assessment of pancreas exocrine function.[15] When low trypsin or fat-soluble vitamin levels are encountered in high-risk individuals, clinicians should discuss initiation of PERT versus stool testing (FE-1 and/or stool fat analysis) to confirm EPI.

Because FE-1 is sometimes used as a stand-alone laboratory assessment for EPI, understanding the limitations of the test is important. The FE-1 test measures human chymotrypsin-like elastases in stool, and should be performed on solid or semi-solid stool.[16] Among patients with a low pre-test probability for EPI, a FE-1 value >200mcg/g has a false negative rate of 1.1%, indicating value as an accurate screening test in this population.[17] In contrast, among individuals with a high pre-test probability, there is a 10% false negative rate, and adjunctive tests in this group should be considered.[17] Alternatively, repeating the FE-1 assessment on a separate occasion may be reasonable.[18] Where available, more elaborate testing may be performed to increase the specificity of the result, such as the malabsorption blood test or 13^C-mixed triglyceride breath test.[14, 19–23] Finally, clinical decision support tools that do not rely on stool-based testing are being developed, but these require additional validation studies prior to widespread adoption.[24, 25]

MANAGEMENT

The management of EPI involves the consumption of exogenous pancreas enzymes, which, at the present time, are nearly all porcine-derived and formulated for oral use.[19] One notable exception is immobilized lipase (Relizorb, [Alcresta Therapeutics, Newton, MA, USA]), which is an in-line lipase-containing cartridge designed for use with enteral feeds.[26] Aside from this advance, there have not been any significant changes to the pharmacology of PERT in the past decade.

Over the past several years, numerous society guidelines have established standards for the use of PERT in CF and CP. Although the CF guidelines are specifically addressing EPI among patients with CF, these have historically been adopted for the management of severe EPI in patients without CF. The CF guidelines highlight several key points in the management of EPI: 1) there is great inter-individual variation in response to enzymes, 2) doses exceeding 2,500 lipase units/kg (body weight)/meal require further investigation (e.g., alternate causes of signs and symptoms, inappropriate enzyme timing in relation to meals, etc.), 3) dosing PERT according to grams of fat ingested is ideal, but not always practical, and 4) fat-soluble vitamin replacement should be commenced simultaneously with PERT.[27, 28] The American College of Gastroenterology recently released a CP guideline, indicating that patients with CP should receive at least 50,000 units of lipase per meal and undergo periodic fat-soluble vitamin screening and bone density measurements.[14] Some guidelines recommend PERT dosing based on body weight,[29] while others recommend PERT based on grams of fat intake.[30] Fat-soluble vitamin replacement has not been widely used in non-CF EPI, which may be related to the lower incidence of deficiencies in these

patients.[31] Notably, both patient- and provider-related factors may contribute to low rates of adherence to EPI guidelines, even in expert centers.[32, 33]

Despite the society guidance statements, a number of uncertainties remain in the management of EPI, including the role of diet changes (high or low fat diet) and specific strategies or methods for titrating and administering PERT dose. It is generally accepted that calories and fat should not be restricted, that PERT dose should be increased until steatorrhea resolves (or until a maximum dose is reached), that PERT may be equally divided to pre-meal and during-meal doses, and that vitamin replacement therapy can be used only when encountering deficiency, although additional studies are warranted to confirm these practices. A recent study evaluated the use of an app-based PERT dose titration strategy among children, and found that some patients with more significant fat malabsorption experienced improvement in CFA with the app-recommended PERT dosages.[34] Furthermore, use of the app reduced heterogeneity of PERT use, such that more individuals consumed approximately 2,000 units of lipase per gram of dietary fat (Figure 1).[34] Additional studies of app-based or education-based interventions to improve PERT titration among individuals with EPD are warranted.

Another challenge in assessing the efficacy of PERT follows directly from the heterogeneity in the diagnosis of EPD. For example, among subjects with a symptom-based diagnosis of diarrhea-predominant irritable bowel syndrome (IBS-D), a recent systematic review determined the pooled prevalence of EPI is 4.6% (range 1.8–6.1%), based on FE-1 <200mcg/g.[35] Among those with IBS-D and proven EPI, treatment with PERT improved stool frequency and consistency, abdominal distension score, pain score, and IBS symptom severity score.[36] Thus, among patients with IBS-D who meet criteria for EPI, treatment with PERT is effective for managing the presenting symptoms. On the other hand, among individuals with GI symptoms (such as diarrhea, abdominal pain, or weight loss) who do not undergo a formal assessment for EPI, administrative claims data indicate that an empiric trial of PERT is usually discontinued within 6 months, suggesting minimal benefits.[37] Alternatively, some individuals may feel that modest benefits do not justify the high costs of PERT.[38] Thus, accurate diagnosis and staging of EPD will facilitate reserving PERT therapy for those with proven EPI and should minimize unnecessary costs for those unlikely to benefit.

PEARLS

Bacterial overgrowth is common and may contribute to EPI.

Small intestinal bacterial overgrowth (SIBO) is prevalent among individuals with exocrine pancreatic disorders and may contribute to signs or symptoms of EPI (bloating, steatorrhea) irrespective of exocrine pancreatic function.[39] Thus, clinicians should maintain a high suspicion for SIBO during the evaluation and management of patients with suspected or confirmed EPD. Excess bacteria in the small bowel deconjugate bile acids, which impair micelle formation and thereby reduce efficacy of pancreatic lipases.[40] This may lead to EPD when pancreas enzyme production is normal, or severe EPI when pancreas enzyme production is reduced.

The pooled prevalence of SIBO in CP is approximately 40%, with the highest risk seen among those with diabetes and EPI.[41, 42] Most subjects in a recent systematic review had persistent EPI symptoms despite optimized PERT dosing, but treatment with rifaximin led to symptom improvement in 86% of subjects, compared to 40% who were treated with doxycycline and metronidazole.[41] Similarly, the prevalence of SIBO in CF is reported to range between 32–56%.[43] A randomized, case-controlled trial was performed among patients with CF and positive glucose breath testing and confirmed that rifaximin (400mg three times daily for 14 days) was effective at eradicating SIBO, with a number needed to treat of 1.75.[43] In contrast to CP, however, abdominal symptoms did not show a significant improvement following treatment with rifaximin. Based on these data, treating SIBO with rifaximin among individuals with EPI may be considered when symptoms persist after PERT is optimized.

Calcium oxalate nephrolithiasis may indicate under-treated EPI.

Enteral hyperoxaluria (EH) refers to the process by which unabsorbed free fatty acids bind to calcium in the intestinal lumen, permitting an increased absorption of dietary oxalate. Once absorbed, oxalate is excreted renally and predisposes to the formation of calcium oxalate nephrolithiasis.[44, 45] The most common causes of EH are post-surgical bypasses (e.g., Roux-en-Y gastric bypass) and disease affecting the small bowel mucosa (e.g., celiac disease, Crohn's disease), but EH can also be identified among patients with EPI, and may contribute to the development of chronic kidney disease or oxalate deposition in other tissues (systemic oxalosis).[45, 46]

The frequency of encountering EH among adults with EPI is not well described, but available data suggest that EH is prevalent among individuals with incompletely treated EPI. One series of adults with CP identified EH in 23% and found that EH was associated with clinical steatorrhea, high levels of fat in the stool, and pancreatic atrophy on imaging.[46] The pooled prevalence of nephrolithiasis in CF is approximately 5%, all of which were calcium oxalate stones, and elevated urine oxalate levels were identified in about half of subjects.[47, 48] Furthermore, poorly controlled EPI is identified as the primary risk factor for the development of nephrolithiasis in CF.[47, 49] Based on these data, patients at-risk for EPI who develop nephrolithiasis should be evaluated for the development of EPI and undergo lifestyle, dietary, and medication interventions to reduce hyperoxaluria, which may include PERT titration.

Treatment of EPI in pancreatic cancer may increase overall survival.

EPI in patients with unresectable or metastatic pancreatic cancer is highly prevalent, and varies according to the location of the primary tumor and length of blockage of the main pancreatic duct.[50, 51] EPI can negatively impact performance status and ability to tolerate anti-neoplastic therapies, and there is emerging evidence that patients with PDAC who receive nutrition interventions (including PERT) have improved overall survival, perhaps due to improved tolerance of therapies.[11, 52] However, the optimal method of diagnosing EPI in pancreatic cancer is currently unknown as FE-1 and clinical symptoms have been demonstrated to be unreliable indicators of EPI in this population.[53] This is currently being studied prospectively (NCT03616431).[51] Based on current data, PERT should be initiated

early for patients with PDAC when EPI is suspected. Delaying PERT until confirmation testing is available may unnecessarily limit access to PERT, with potentially negative implications for overall survival.

EPI may be a late consequence of immunotherapy.

Several pancreatic immune related adverse events (iRAEs) have been described following immune checkpoint inhibitor (ICI) therapy, including ICI-related AP and ICI-related EPI.[54] The mechanism of ICI-related EPI is thought to involve CD8+ T cells damaging cellular components of the exocrine pancreas.[54] Interestingly, ICI-related pancreatic atrophy may be yet another distinct clinical entity, as pancreatic atrophy and EPI after ICI therapy did not correlate in one case-control study.[55] As more long-term follow up data becomes available, our understanding of pancreatic iRAEs is likely to improve. At this time, a high index of suspicion for EPD after ICI therapy is necessary. In order to diagnose ICI-related EPI, non-pancreatic causes (such as ICI-related colitis or enteritis) should be investigated and excluded.

PITFALLS

PERT works best when taken appropriately.

Making an accurate diagnosis of EPI is necessary prior to considering PERT therapy. At present, few patients at high risk for EPI (e.g., CP, pancreatic cancer) undergo formal testing for EPI, which leads to under-recognition of EPI and may contribute to the development of more severe nutritional complications.[33] After EPI is diagnosed, PERT is prescribed to improve the digestion of dietary fats and proteins, to improve nutrient absorption, and to alleviate the symptoms that accompany malabsorption. One way of illustrating this would be to suggest that PERT treats the fats and proteins in foods, and therefore must be taken along with meals. As patients develop an understanding of this rationale, the need for prandial dosing becomes evident and adherence to treatment will improve.

An initial dose of at least 50,000 units lipase with meals and 25,000 with snacks should be provided.[14] Depending on the patient's capacity and engagement, additional layers of education can be provided in order to optimize consumption of PERT. PERT is inactivated rapidly by gastric acidity, so the timing in relation to meals is of great importance and PPI therapy may be reasonable to extend the effective duration of PERT. For patients who are consuming larger number of enzyme capsules (e.g., ≥6), switching to a higher dose (e.g., from 12,000 to 36,000 unit capsule) or splitting the dose into a pre-meal portion and during-meal portion are viable options to mitigate the pill burden. If steatorrhea persists, selectively increasing PERT by 1–2 capsules for high fat or high protein meals is an appropriate step in PERT titration. Some patients may be interested in titrating PERT mathematically (e.g., 2,000 units of lipase per gram of fat), and consultation with a registered dietician can facilitate this level of education. Patients should be encouraged to keep food journals accompanied by PERT dosing and gastrointestinal symptoms to aide this discussion and titration.

Cognitive biases may interfere with an accurate assessment of EPI.

Measuring FE-1 is often performed in the evaluation of chronic diarrhea. In this context, the FE-1 result should be interpreted with caution as a watery stool is known to dilute the stool and lead to a falsely low FE-1 value.[10] Additionally, a value <200mcg/g is often labelled abnormal on the laboratory result, although this is not specific for EPD, and patients and clinicians may develop an *anchoring bias* on the diagnosis of EPD. Next, a *commission bias* occurs: clinicians may believe that it is better to err on the side of PERT therapy than err on the side of no treatment. Perhaps the patient is a smoker, or consumed alcohol previously: these historical features are now used to support a diagnosis of CP as an explanation for EPI, which represents *confirmation bias*.[56] Instead, when EPD is suspected, providing the patient with clear instructions about the need for an adequate specimen (e.g., formed stool) and clarifying the performance characteristics of FE-1 testing is warranted to avoid anxiety and extraneous testing. Finally, if a patient fails to respond to a therapeutic PERT dose and/or requests to switch formulations, this may indicate that EPD is not the underlying cause of the presenting symptoms.

Pancreatic atrophy and diarrhea: a clinical challenge.

Pancreatic atrophy, pancreatic lipomatosis, and fatty pancreas are terms used to describe an abnormal appearing pancreas on cross sectional imaging.[57] This may be seen with age, after recovery from AP, in metabolic conditions (e.g., metabolic syndrome, type 1 diabetes), with genetic syndromes (e.g., *CEL*), or after exposure to certain medications.[57] When pancreatic lipomatosis and diarrhea or steatorrhea co-exist, the pre-test probability for EPI is difficult to estimate but is likely higher among individuals with pancreatic atrophy than among those with a structurally normal pancreas. Therefore, we advocate for a thorough evaluation for non-pancreatic causes of diarrhea in tandem with indirect pancreas function testing (typically FE-1) and assessment of fat-soluble vitamin levels. Diabetic exocrine pancreatopathy may be seen in type 1 diabetes and can cause decreased FE-1, but rarely results in overt EPI.[58] When a pancreatic etiology is suspected in a patient older than 50 years, an endoscopic ultrasound with direct pancreatic function testing would be a reasonable test to assess for structural evidence of CP or pancreatic cancer.[59] For patients younger than 50, additional non-invasive assessments can be performed, such as serial FE-1 measurements or 72-hour fecal fat collection. If EPI is confirmed, then further diagnostic evaluation to identify the underlying etiology (e.g., genetic testing) may be indicated.

CONCLUSIONS

At present, the most widely used clinical test for diagnosing EPI is the FE-1 assay. While this is straightforward to collect and reasonably accurate, there remains a need for more specific tests of pancreatic exocrine function and fat malabsorption in order to improve recognition and management of EPI. Until more specific tests are available, EPD will remain a heterogeneous patient population, encompassing patients with celiac disease, SIBO, pancreatic disorders, and other conditions. Among patients with EPD, many will benefit symptomatically from PERT, but more specific and less expensive therapies may be more appropriately used before initiating PERT. Among patients with confirmed EPI, PERT will be necessary and should be titrated to alleviate symptoms and normalize fat absorption.

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Key Points:

- Exocrine pancreatic dysfunction (EPD) exists on a spectrum and individuals with severe EPD are most likely to benefit from pancreas enzyme replacement therapy (PERT).
- Milder EPD may be seen in a number of conditions, including celiac disease or bacterial overgrowth, which may be successfully managed without PERT.
- Fat-soluble vitamin deficiencies and nephrolithiasis may indicate severe fat malabsorption and can complement stool-based testing for EPD.

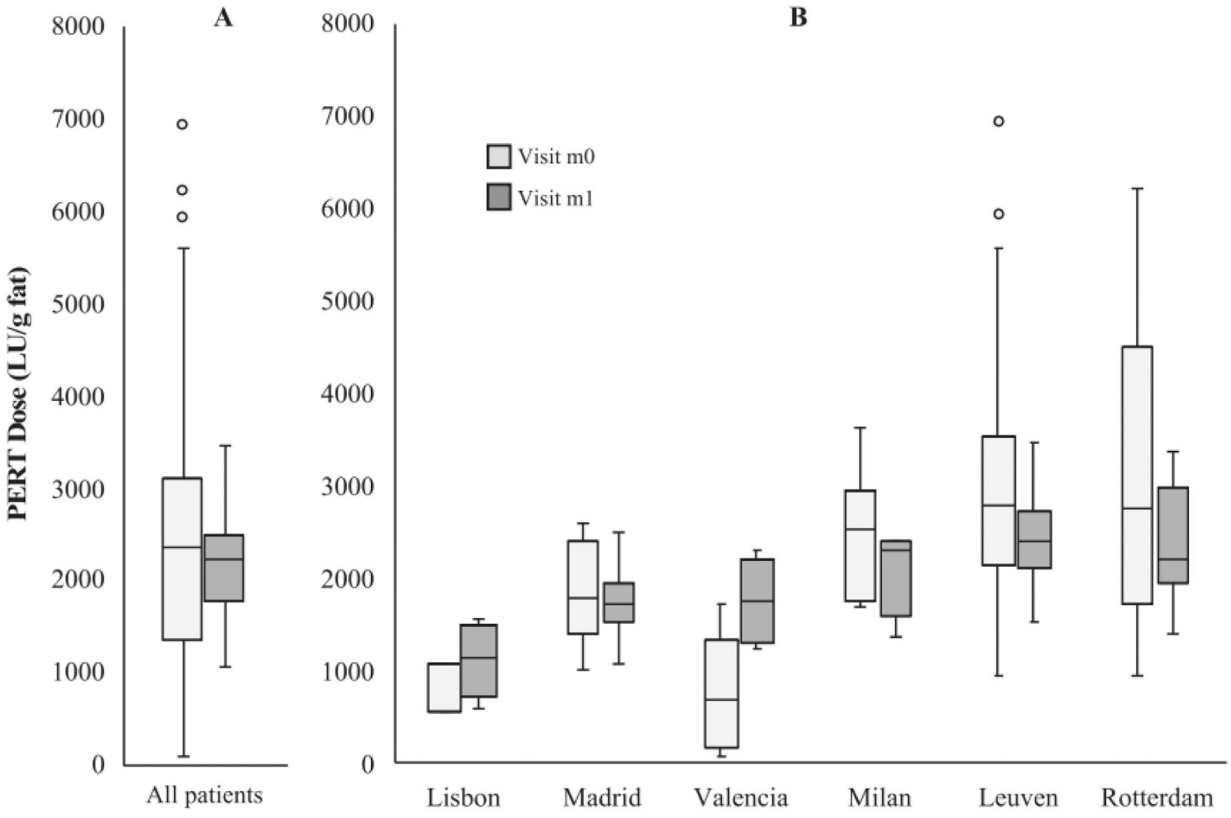

Figure 1:

Change in PERT dose measured in units of lipase according to grams of dietary fat before and after use of a PERT dosing application. Used with permission from Calvo Lerma, et al.[34]

Table 1 –

Staging of exocrine pancreatic dysfunction, adapted from Khan, et al.[2]

	Descriptive terminology	FE-1 levels (mcg/gm)	Coefficient of fat absorption (%)	Symptoms	Serum vitamin A and E levels	PERT indicated?
Stage I	Mild exocrine pancreatic dysfunction	100–200	≥93	None	Normal	NO
Stage II	Moderate pancreatic exocrine dysfunction	<100	≥93[a]	None	Normal	NO
Stage III	Severe pancreatic exocrine dysfunction (EPI without micronutrient deficiency)	<100 (usually <50)	<85[a]	Usually present	Normal / low normal	YES
Stage IV	Severe pancreatic exocrine dysfunction (EPI with micronutrient deficiency)	<100 (usually <50)	<85	Usually present	Low	YES and consider micronutrient supplementation

[a]Patients with CFA <93 but >95 would fall into severe EPD if they had symptoms responsive to PERT or low normal vitamin levels. In the absence of these features, such patients can be managed without PERT.

Abbreviations: exocrine pancreatic insufficiency (EPI); fecal elastase (FE-1) pancreas enzyme replacement therapy (PERT)

Table 2 –

Differential diagnosis for exocrine pancreatic dysfunction along with diagnostic testing strategies and treatment alternatives or complements to pancreatic enzyme replacement therapy.

	Evaluation	**Treatments to consider other than PERT**
Decreased pancreas exocrine function or drainage		
Acute pancreatitis	History	
Chronic pancreatitis	History, imaging	
Pancreatic cancer	History, imaging	
Pancreatic resection	History, imaging	
Genetic and congenital disorders:	History, genetic testing	
Cystic fibrosis, *CFTR*-related disorders	Genetic testing	Exocrine function may improve with CFTR modulators
Schwachman-Diamond syndrome	Genetic testing	
Johanson-Blizzard syndrome	Genetic testing	
Pancreatic agenesis	Imaging	
Wilson's disease	Serum ceruloplasmin, 24-hour urine copper	Chelation therapy
Hemochromatosis	Iron studies, genetic testing	Therapeutic phlebotomy
Post-cibal asynchrony (disordered mixing and/or altered hormone secretion)		
Gastric resections and other foregut surgery	Surgical history, imaging	Dietary changes, open-capsule or uncoated PERT
Crohn's disease with enteritis	Imaging, endoscopy	Treat underlying cause
Celiac disease	Serology and small intestine biopsy	Gluten free diet
Diabetes mellitus	History and glucose lab values	
Other disorders with maldigestion or malabsorption of fats		
Gastrinoma (Zollinger-Ellison Syndrome)	Fasting gastrin level	Treat underlying cause
Cholestatic disorders (e.g., primary sclerosing cholangitis)	Liver function tests and imaging	Fat soluble vitamin supplementation
Medications (orlistat, purgative use to facilitate eating disorder)	History	Discontinue use
Short bowel syndrome	History, imaging	Dietary changes, treat underlying cause
Intestinal lymphangiectasia	Cardiac and/or lymphatic imaging	Treat underlying cause
Genetic and congenital disorders		
Abetalipoproteinemia	Genetic testing	Dietary changes
Hypobetalipoproteinemia	Genetic testing	Dietary changes
Infections		
Giardia	Stool assay	Antibiotics (e.g., metronidazole)
Whipple's disease (*Trophyerma whipplei)*	Small bowel biopsy	Antibiotics (e.g., ceftriaxone then TMP-SMX)
Bacterial overgrowth	Breath testing or empiric therapy	Antibiotics (e.g., rifaximin)

Abbreviations: exocrine pancreatic insufficiency (EPI), pancreas enzyme replacement therapy (PERT),