JAMA Insights

Exocrine Pancreatic Insufficiency

Mitchell L. Ramsey, MD; Christopher E. Forsmark, MD

Exocrine pancreatic insufficiency is defined by a loss of pancreatic enzyme production or delivery sufficient to cause clinically significant maldigestion (defective intraluminal breakdown of dietary nutrients).[1,2] Approximately 10% of the normal output of pancreatic enzymes is sufficient to prevent fat maldigestion.[2] Less severe loss, which does not cause maldigestion, is termed *exocrine pancreatic dysfunction*.[1] Exocrine insufficiency is most frequently caused by loss of pancreatic tissue, which reduces enzyme synthesis. The most common causes of exocrine insufficiency are cystic fibrosis (>85% of patients are affected), chronic pancreatitis (>50%, depending on etiology and duration), acute pancreatitis[3] (19% after a mild episode; 33% after a severe episode), blockage of the pancreatic duct preventing enzyme delivery as may occur with pancreatic cancer (50%-90%), and undergoing pancreatic surgery.[2,4] Less common causes include defective mixing of food and enzymes after intestinal surgery or duodenal diseases, such as celiac disease, which interfere with hormonal signaling for pancreatic secretion.

Clinical Presentation

The clinical manifestations of exocrine pancreatic insufficiency vary. Visible fat in stool (steatorrhea), weight loss, sarcopenia (loss of skeletal muscle), and nutrient deficiency (particularly vitamins D and A) are observed in those with severe or long-standing insufficiency.[2] These symptoms do not differentiate pancreatic maldigestion from other causes of malabsorption such as celiac disease or small intestinal bacterial overgrowth. Symptoms may also include bloating and excess flatulence. Patients may note oil or grease in the stool or toilet water and malodorous stools, but watery diarrhea is rarely observed. Patients may develop osteopenia or osteoporosis (up to two-thirds of patients with chronic pancreatitis) as a consequence of vitamin D deficiency. Because patients are often reluctant to discuss stool character, eliciting these symptoms may require clinician-initiated discussion.

Diagnosis

The diagnosis of exocrine pancreatic insufficiency is based on presence of both fat malabsorption and decreased pancreatic exocrine function. The American Gastroenterological Association recommends the fecal elastase-1 test as the most appropriate initial test for diagnosing exocrine pancreatic insufficiency because it is simple, noninvasive, and relatively inexpensive (**Table**).[2,5] A normal elastase level is greater than 200 µg/g of stool. Although fecal elastase can be measured on a single stool sample and is unaffected by pancreas enzyme therapy, there is variability from sample to sample, and testing a very loose or watery stool sample can produce a false-positive result due to dilution. Therefore, the result must be interpreted in the context of the pretest probability of exocrine insufficiency, which incorporates patient history (eg, presence and severity of prior acute pancreatitis; presence of chronic pancreatitis, cystic fibrosis, or pancreatic cancer; type of pancreatic surgery [particularly pancreatic resection]), symptoms (eg, steatorrhea, weight loss), pancreatic imaging features (eg, dilated pancreatic duct, calcifications, atrophy, or mass on computed tomographic scan or magnetic resonance imaging), and consistent laboratory values (eg, low serum lipase, low fat-soluble vitamin levels). In a systematic review and meta-analysis of 13 observational cohort studies (7 cystic fibrosis, 4 chronic pancreatitis, 1 diabetes, 1 pancreatic surgery) of 888 patients comparing fecal elastase with quantitative measurement of fecal fat, the sensitivity of fecal elastase less than 200 µg/g of stool was 0.94, with a specificity of 0.69.[5] Using a more stringent cutoff of elastase of less than 100 µg/g of stool, the sensitivity was 0.88 and specificity was 0.82. The moderate specificity leads to a substantial false-positive result rate when fecal elastase testing is used in low-prevalence populations. Clinicians should avoid diagnosing exocrine insufficiency based

Table. American Gastroenterology Guideline Recommendations for Diagnosis and Treatment of Exocrine Pancreatic Insufficiency

Topic	Guideline best practice	Caveat
Focus testing for exocrine pancreatic insufficiency on those with sufficient pretest probability	Patients with pretest probability ≥25%: Those with a history of acute or chronic pancreatitis, pancreatic cancer, previous pancreatic surgery, cystic fibrosis Abnormal computed tomographic scan with pancreatic atrophy, calcification, or a dilated pancreatic duct Steatorrhea with or without fat-soluble vitamin deficiency	The pancreas has substantial excess capacity; significant loss or damage is required before insufficiency develops Avoid testing in patients with low pretest probability due to risk of false-positive result; consider alternative diagnoses
Fecal elastase testing should be performed and interpreted correctly	Sample must be performed on a solid or semisolid stool specimen Patients do not need to stop pancreatic enzyme treatment for testing Test is variable; repeat testing may be informative Cutoff for the test is 200 µg/g of stool, but a cutoff of 100 µg/g is more specific (pooled sensitivity and specificity of 0.94 and 0.69, respectively, for cutoff of 200 µg/g and 0.88 and 0.82, respectively, for cutoff of 100 µg/g)	Testing watery stool will lead to dilution of elastase and false-positive result A low elastase alone is insufficient to diagnose exocrine insufficiency Low levels of elastase can be seen in those without clinical exocrine insufficiency (eg, in patients with diabetes, older age [>65 y], celiac disease, irritable bowel syndrome, and others)
When using pancreatic enzyme therapy, use the most effective dose and timing	A starting dose of ≥40 000-50 000 units of lipase per meal, and half that with snacks The dose may be increased depending on response, with typical doses approximately 70 000-100 000 units/meal Administer the enzymes during the meal	Individuals requiring very high doses, eg, 10 000 units of lipase per kg of body weight per day, should be reassessed for alternate diagnoses Over-the-counter products have variable and unpredictable potency and efficacy
When using enzyme replacement, measure baseline nutrient levels, supplement as needed, and monitor these over time	Fat-soluble vitamins (A, D, E, K; yearly) Anthropometrics (body mass index, muscle strength and function; yearly) Glycated hemoglobin (yearly) Bone density scan (every 1-2 y)	Consider routine A, D, E, and K supplementation; monitor levels annually to ensure no deficiency or toxicity Consider measuring B vitamins, folate, and micronutrients (zinc, magnesium, calcium) at baseline

on elastase values alone; clinical and imaging features should also be assessed. Fecal elastase should not be part of the initial testing for chronic diarrhea because infectious, inflammatory, and drug-induced causes are more common. Cross-sectional imaging may be performed to identify underlying pancreatic abnormalities associated with exocrine pancreatic insufficiency.

The differential diagnosis includes irritable bowel syndrome with diarrhea, microscopic colitis, and nonpancreatic causes of steatorrhea such as celiac disease and small intestinal bacterial overgrowth.[2,4] Patients with type 1 and 2 diabetes, which can cause both diarrhea and an atrophic or fatty pancreas, may require consultation with a gastroenterologist to distinguish exocrine pancreatic insufficiency from diabetes-associated diarrhea.[6] Although gastrointestinal symptoms associated with conditions in the differential diagnosis can mimic exocrine insufficiency and may partially respond to pancreatic enzyme replacement therapy, they should be treated with more effective disease-specific treatments.

Treatment

First-line treatment of exocrine pancreatic insufficiency is lifelong prandial consumption of exogenous digestive enzymes. The current US Food and Drug Administration–approved pancreatic enzyme–replacement formulations are derived from porcine sources; most are enteric-coated and formulated for oral use. One pancreatic enzyme replacement is uncoated (and should be used with acid suppression to prevent lipase inactivation) and 1 is formulated to facilitate lipolysis with tube-based enteral nutrition. For enteric coated formulations, the adult starting dose is approximately 40 000 to 50 000 units of lipase with each meal and 25 000 units of lipase with each snack.[2,7] Alternatively, enzyme dose may be guided by dietary grams of fat (2500 to 4000 units of lipase per gram of dietary fat); this dosing strategy is used primarily in children.[7] The pancreatic enzyme replacement dose is typically adjusted to achieve symptom control and relief of steatorrhea or titrated up to a maximum of 10 000 units of lipase per kg of body weight per day. Maximum dosage is rarely prescribed except for patients with cystic fibrosis. Doses higher than 10 000 units of lipase per kg of body weight per day increase the risk of fibrosing colonopathy (scar formation in the colon leading to obstruction), a rare (0.024 per 1000 person-years) adverse effect of enzyme replacement in cystic fibrosis.[8]

Although current pancreatic enzyme replacements achieve symptom relief (decreased stool frequency and visible fat in stool) in approximately 75% of patients with exocrine pancreatic insufficiency, they do not fully correct digestion and absorption. Patients may therefore develop long-term sequelae of insufficiency including fat-soluble vitamin deficiency and metabolic bone disease.[8,9] Per 2023 guidelines, all individuals with exocrine insufficiency should undergo annual nutrition assessment, including a review of adherence to pancreatic enzyme administration, evaluation of skeletal muscle mass and function (eg, grip strength), and laboratory assessment of fat-soluble vitamin (A, D, E, and K) and micronutrient levels (B_{12}, thiamine, folate, magnesium, selenium, zinc, and iron studies).[2] Bone densitometry should be assessed periodically, generally every 1 to 2 years, due to high prevalence of osteoporosis (18%) and osteopenia (39%).[10] Patients with vitamin or micronutrient deficiencies should take fat-soluble vitamins and/or a combination multivitamin with other micronutrients (zinc, B vitamins, magnesium, calcium); doses can be titrated based on annual levels. For patients with persistently low micronutrient levels who are taking the prescribed micronutrients and vitamins consistently and correctly (during meals), clinicians should consider alternative causes and increase the doses of micronutrients and vitamins.

Conclusions

Exocrine pancreatic insufficiency most commonly occurs in individuals with a history of cystic fibrosis, acute or chronic pancreatitis, pancreatic cancer, or pancreatic surgery, and may cause metabolic bone disease, sarcopenia, and fat-soluble vitamin deficiencies. Fecal elastase-1 is the most appropriate initial test for diagnosis of exocrine pancreatic insufficiency. First-line treatment involves pancreatic enzyme–replacement therapy, typically lifelong, and ongoing monitoring with vitamin levels and bone density studies.

ARTICLE INFORMATION

Author Affiliations: Division of Gastroenterology, Hepatology, and Nutrition, Department of Internal Medicine, The Ohio State University Wexner Medical Center, Columbus (Ramsey); Division of Gastroenterology, Hepatology, and Nutrition, University of Florida, Gainesville (Forsmark).

Corresponding Author: Christopher E. Forsmark, MD, University of Florida, 1329 SW 16th St, Ste 5251, Box 100214, Gainesville, FL 32610-0214 (chris.forsmark@medicine.ufl.edu).

Published Online: June 10, 2026. doi:10.1001/jama.2026.5759

Conflict of Interest Disclosures: Dr Ramsey reported receiving grants from American Society of Parenteral and Enteral Nutrition and Cystic Fibrosis Foundation and personal fees from Nestle Health Sciences outside the submitted work. No other disclosures were reported.

REFERENCES

1. Khan A, Vege SS, Dudeja V, Chari ST. Staging exocrine pancreatic dysfunction. *Pancreatology*. 2022;22(1):168-172. doi:10.1016/j.pan.2021.11.005

2. Whitcomb DC, Buchner AM, Forsmark CE. AGA Clinical Practice Update on the epidemiology, evaluation, and management of exocrine pancreatic insufficiency: expert review. *Gastroenterology*. 2023;165(5):1292-1301. doi:10.1053/j.gastro.2023.07.007

3. Eperjesi O, Bucur M, Rancz A, et al. Risk factors for pancreatic exocrine insufficiency after acute pancreatitis. *Pancreatology*. 2026;26(3):404-411. doi:10.1016/j.pan.2026.03.001

4. Ramsey ML, Hart PA, Forsmark CE. Evaluation and management of exocrine pancreatic insufficiency: pearls and pitfalls. *Curr Opin Gastroenterol*. 2023;39(5):428-435. doi:10.1097/MOG.0000000000000951

5. de la Iglesia D, Agudo-Castillo B, Galego-Fernández M, Rama-Fernández A, Domínguez-Muñoz JE. Diagnostic accuracy of fecal elastase-1 test for pancreatic exocrine insufficiency. *United European Gastroenterol J*. 2025;13(8):1571-1582. doi:10.1002/ueg2.70061

6. Mohapatra S, Majumder S, Smyrk TC, et al. Diabetes mellitus is associated with an exocrine pancreatopathy: conclusions from a review of literature. *Pancreas*. 2016;45(8):1104-1110. doi:10.1097/MPA.0000000000000609

7. Ramsey ML, Galante GJ. Pancreas and pancreatitis: exocrine pancreatic insufficiency. *Pediatr Pulmonol*. 2024;59(suppl 1):S44-S52. doi:10.1002/ppul.27013

8. Chiuve SE, Fife D, Leitz G, et al. Incidence of fibrosing colonopathy with pancreatic enzyme replacement therapy in patients with cystic fibrosis. *J Cyst Fibros*. 2023;22(6):1017-1023. doi:10.1016/j.jcf.2023.08.013

9. Duggan SN, Smyth ND, O'Sullivan M, Feehan S, Ridgway PF, Conlon KC. The prevalence of malnutrition and fat-soluble vitamin deficiencies in chronic pancreatitis. *Nutr Clin Pract*. 2014;29(3):348-354. doi:10.1177/0884533614528361

10. Ramai D, Facciorusso A, Maida M, et al. Prevalence of osteopathy in chronic pancreatitis. *Clin Transl Gastroenterol*. 2023;14(8):e00623. doi:10.14309/ctg.0000000000000623