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Explore EPI

What is Exocrine Pancreatic Insufficiency (EPI)?

EPI Is Associated With Conditions That Affect Production, Delivery, or Activity of Pancreatic Enzymes

Exocrine pancreatic insufficiency (EPI) is a condition characterized by the deficiency of the exocrine pancreatic enzyme below the threshold required for normal digestion.¹²

Decreased Production ²							Decreased Delivery ²	Decreased Activity ^{2*}	
				Loss of pancreatic parenchyma			Pancreatic duct obstruction	Poor mixing of pancreatic enzymes, postprandial asynchrony, low duodenal pH	
Predisposing condition ²									
Cystic fibrosis	Chronic pancreatitis	Acute pancreatitis	Pancreatic resection	Type 1 diabetes	Crohn's disease	Untreated celiac	Pancreatic tumor	Pancreatic resection	Gastric resection
Percentage of patients who experienced EPI									
Up to 90% ³	Increases with CP duration ⁴	27–35% ^{5,6}	Variable ^{7,8}	26–44% ²	14–30% ⁹	11–25% ^{16,17}	Unresectable pancreatic cancer, 50–92% ^{10,11} Resectable pancreatic cancer, 55–89% ^{12,14}	Variable ^{7,8}	Roux-en-Y gastric bypass, 31% ¹⁵

*Despite normal secretion.

EPI=exocrine pancreatic insufficiency. CP=chronic pancreatitis.

1. Lindkvist B. Diagnosis and treatment of pancreatic exocrine insufficiency. *World J Gastroenterol*. 2013;19:7258–7266. 2. Othman MO, Harb D, Barkin JA. Introduction and practical approach to exocrine pancreatic insufficiency for the practicing clinician. *Int J Clin Pract*. 2018;72(2):e13066. 3. Walkowiak J, Sands D, Nowakowska A, et al. Early decline of pancreatic function in cystic fibrosis patients with class 1 or 2 CFTR mutations. *J Pediatr Gastroenterol Nutr*. 2005;40(2):199–201. 4. Kempeneers MA, Ahmed Ali U, Issa Y, et al. Natural course and treatment of pancreatic exocrine insufficiency in a nationwide cohort of chronic pancreatitis. *Pancreas*. 2020;49(2):242–248. 5. Hollemans RA, Hallensleben NDL, Mager DJ, et al. Pancreatic exocrine insufficiency following acute pancreatitis: systematic review and study level meta-analysis. *Pancreatol*. 2018;18(3):253–262. 6. Huang W, de la Iglesia-García D, Baston-Rey I, et al. Exocrine pancreatic insufficiency following acute pancreatitis: systematic review and meta-analysis. *Dig Dis Sci*. 2019;64(7):1985–2005. 7. Lim PW, Dinh KH, Sullivan M, et al. Thirty-day outcomes underestimate endocrine and exocrine insufficiency after pancreatic resection. *HPB (Oxford)*. 2016;18(4):360–366. 8. Sabater L, Ausania F, Bakker OJ, et al. Evidence-based guidelines for the management of exocrine pancreatic insufficiency after pancreatic surgery. *Ann Surg*. 2016;264(6):949–958. 9. Singh VK, Haupt ME, Geller DE, Hall JA, Quintana Diez PM. Less common etiologies of exocrine pancreatic insufficiency. *World J Gastroenterol*. 2017;23(39):7059–7076. 10. Sikkens EC, Cahen DL, de Wit J, Looman CWN, van Eijck C, Bruno MJ. A prospective assessment of the natural course of the exocrine pancreatic function in patients with a pancreatic head tumor. *J Clin Gastroenterol*. 2014;48(5):e43–e46. 11. Partelli S, Frulloni L, Minniti C, et al. Faecal elastase-1 is an independent predictor of survival in advanced pancreatic cancer. *Dig Liver Dis*. 2012;44(11):945–51. 12. Belyaev O, Herzog T, Chromik AM, Meurer K, Uhl W. Early and late postoperative changes in the quality of life after pancreatic surgery. *Langenbecks Arch Surg*. 2013;398(4):547–555. 13. Sikkens EC, Cahen DL, de Wit J, Looman CW, van Eijck C, Bruno MJ. Prospective assessment of the influence of pancreatic cancer resection on exocrine pancreatic function. *Br J Surg*. 2014;101(2):109–113. 14. Halloran CM, Cox TF, Chauhan S, et al. Partial pancreatic resection for pancreatic malignancy is associated with sustained pancreatic exocrine failure and reduced quality of life: a prospective study. *Pancreatol*. 2011;11(6):535–545. 15. Borbély Y, Plebani A, Kröll D, Ghisla S, Nett PC. Exocrine pancreatic insufficiency after Roux-en-Y gastric bypass. *Surg Obes Relat Dis*. 2016;12(4):790–794. 16. Leeds JS, Hopper AD, Hurlstone DP, et al. Is exocrine pancreatic insufficiency in adult coeliac disease a cause of persisting symptoms? *Aliment Pharmacol Ther*. 2007;25(3):265–271. doi:10.1111/j.1365-2036.2006.03206.x 17. Vujasinovic M, Tepes B, Volfand J, Rudolf S. Exocrine pancreatic insufficiency, MRI of the pancreas and serum nutritional markers in patients with coeliac disease. *Postgrad Med J*. 2015;91(1079):497–500. doi:10.1136/postgradmedj-2015-133262

Underlying Conditions Potentially Associated With EPI

Although EPI is most commonly associated with conditions that damage the pancreatic parenchyma (ie, chronic pancreatitis, pancreatic surgery, pancreatic cancer), other conditions may also play a role in the development of EPI.

Exocrine Pancreatic Insufficiency (EPI) may be present in patients with the following underlying conditions and procedures:

CYSTIC FIBROSIS

CHRONIC PANCREATITIS

PANCREATECTOMY

Other underlying conditions and procedures in which EPI has been reported include:

ACUTE PANCREATITIS

CELIAC DISEASE

CROHN'S DISEASE

GASTRIC SURGERY

PANCREATIC CANCER

TYPE 1 DIABETES

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Cystic Fibrosis

CF Affects Approximately 30,000 People in the US¹

Cystic fibrosis transmembrane conductance regulator (CFTR)²⁻⁶

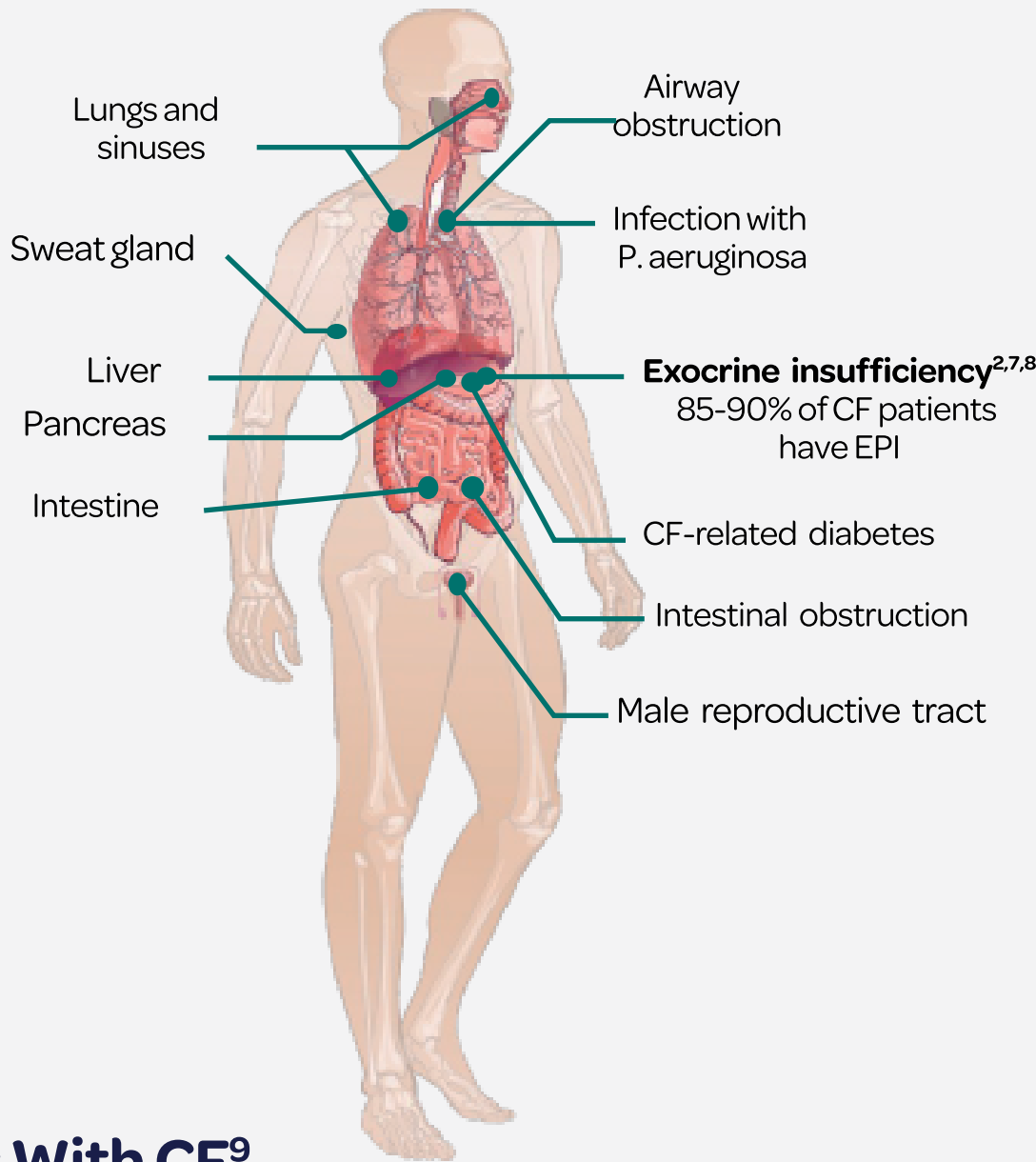
- Regulates the efflux of Cl⁻ and HCO₃⁻
- Controls exocrine fluid Na⁺, osmolality, pH, viscosity, and volume

CFTR gene mutation²⁻⁶

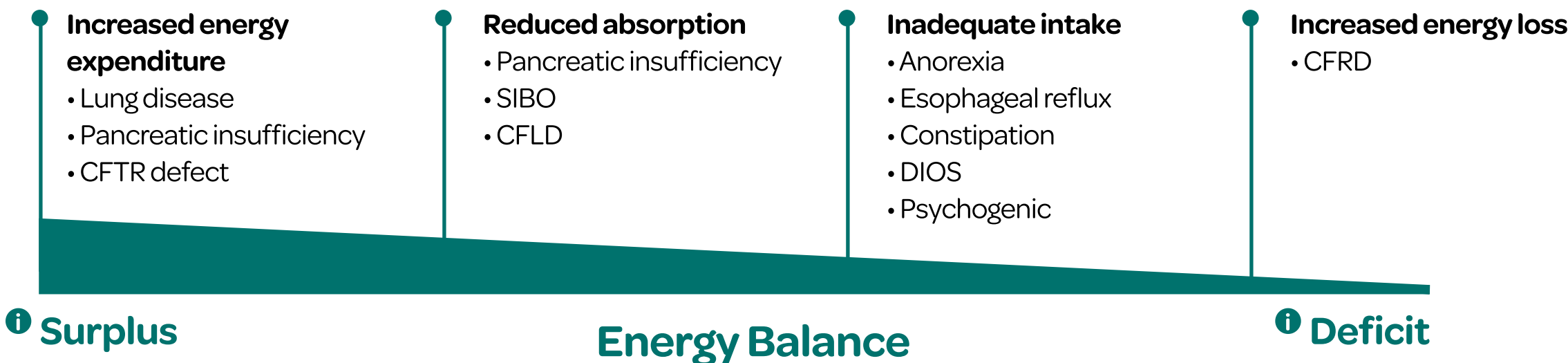
- Impaired CFTR protein function or absence of protein
- Disruption of ductal fluid secretion and generation of thick mucus

Nutritional Status Is Critical in Patients With CF⁹

- Pulmonary function (FEV1% predicted) was much lower in adult patients with CF when weight-for-age percentile (WAP) was <10% at age 4 years
- Greater weight percentile at age 4 years is associated with better survival through age 18 years
 - As weight percentile increases, the proportion for survival also increases



Pathogenesis of Disordered Nutrition in CF¹⁰



CFLD=CF liver disease. CFRD=CF-related diabetes. DIOS=distal intestinal obstruction syndrome. SIBO=small intestinal bacterial overgrowth. PI=pancreatic insufficient. PS=pancreatic sufficient.

1. Cystic Fibrosis Foundation Patient Registry. 2018 Patient Registry Annual Data Report 2018; 2019. 2. Knowles MR. What is cystic fibrosis? *N Engl J Med*. 2002;347(6):439-442. 3. Wilschanski M. Patterns of GI disease in adulthood associated mutations in the CFTR gene. *Gut*. 2007;56(8):1153-1163. 4. Martiniano SL. Cystic fibrosis: a model system for precision medicine. *Curr Opin Pediatr*. 2016;28(3):312-317. 5. Borowitz D. CFTR, bicarbonate, and the pathophysiology of cystic fibrosis. *Pediatr Pulmonol*. 2015;50(suppl 40):S24-S30. 6. Frizzell RA. Physiology of epithelial chloride and fluid secretion. *Cold Spring Harb Perspect Med*. 2012;2(6):a009563. 7. O'Sullivan BP. Cystic fibrosis. *Lancet*. 2009;373:1891-1904. 8. Cutting GR. Cystic fibrosis genetics: from molecular understanding to clinical application. *Nat Rev Genet*. 2015;16(1):45-56. 9. Yen EH. Better nutritional status in early childhood is associated with improved clinical outcomes and survival in patients with cystic fibrosis. *J Pediatr*. 2013;162(3):530-535. 10. Solomon M. Nutritional Issues in Cystic Fibrosis. *Clin Chest Med*. 2016;37(1):97-107. 11. Pallagi P. The Physiology and Pathophysiology of Pancreatic Ductal Secretion: The Background for Clinicians. *Pancreas*. 2015;44(8):1211-1233. 12. Bardeesy N. Pancreatic cancer biology and genetics. *Nat Rev Cancer*. 2002;2:897-909. 13. Culhane S. Malnutrition in cystic fibrosis: a review. *Nutr Clin Pract*. 2013;28(6):676-683. 14. Sathe MN. Gastrointestinal, Pancreatic, and Hepatobiliary Manifestations of Cystic Fibrosis. *Pediatr Clin North Am*. 2016;63(4):679-98. 15. Stevens T. Pathogenesis of chronic pancreatitis: an evidence-based review of past theories and recent developments. *Am J Gastroenterol*. 2004;99(11):2256-2270. 16. Borowitz D. Gastrointestinal outcomes and confounders in cystic fibrosis. *J Pediatr Gastroenterol Nutr*. 2005;41(3):273-85. 17. Schindler T. Nutrition Management of Cystic Fibrosis in the 21st Century. *Nutr Clin Pract*. 2015;30(4):488-500.

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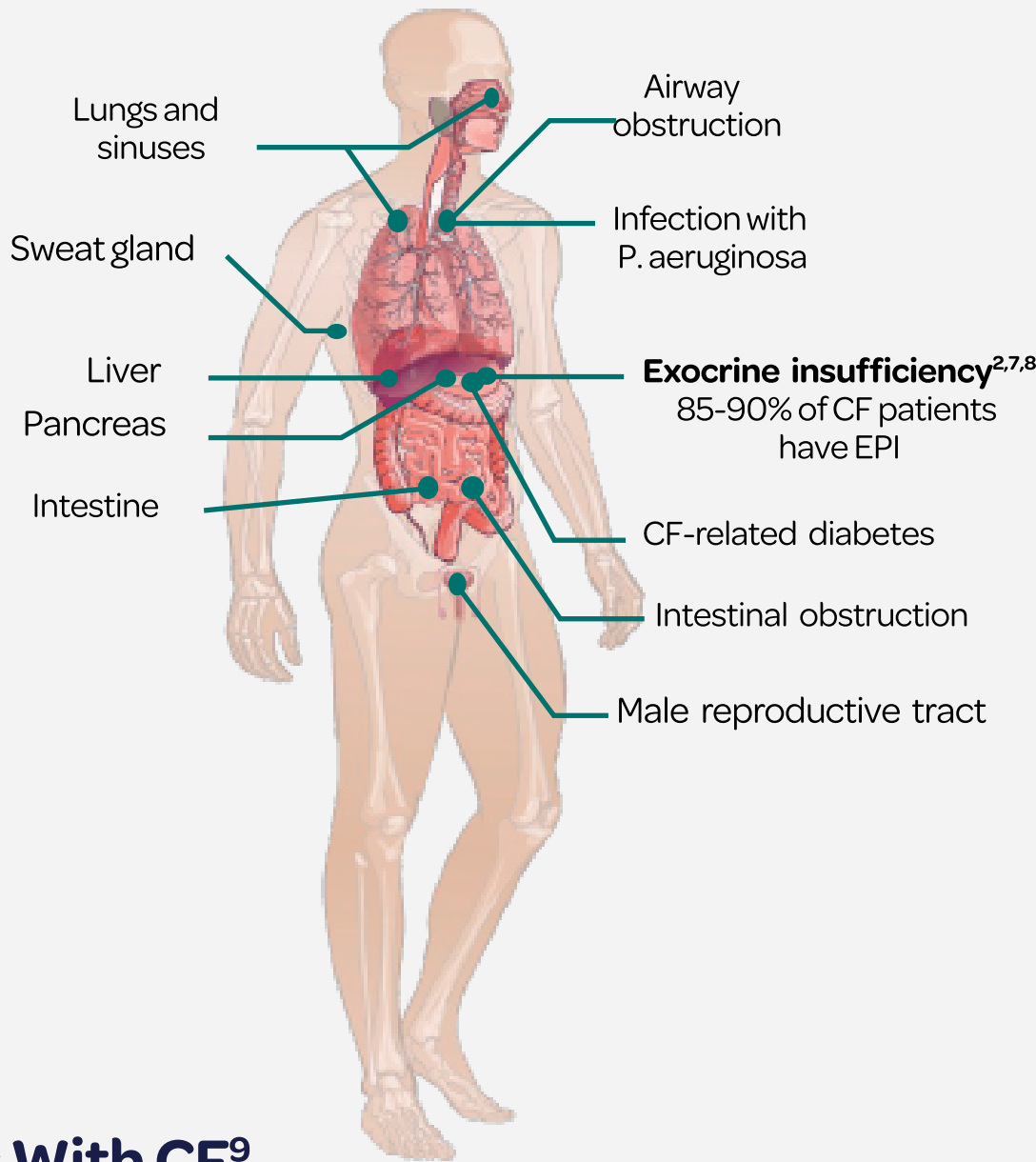
- Regulates the efflux of Cl⁻ and HCO₃⁻
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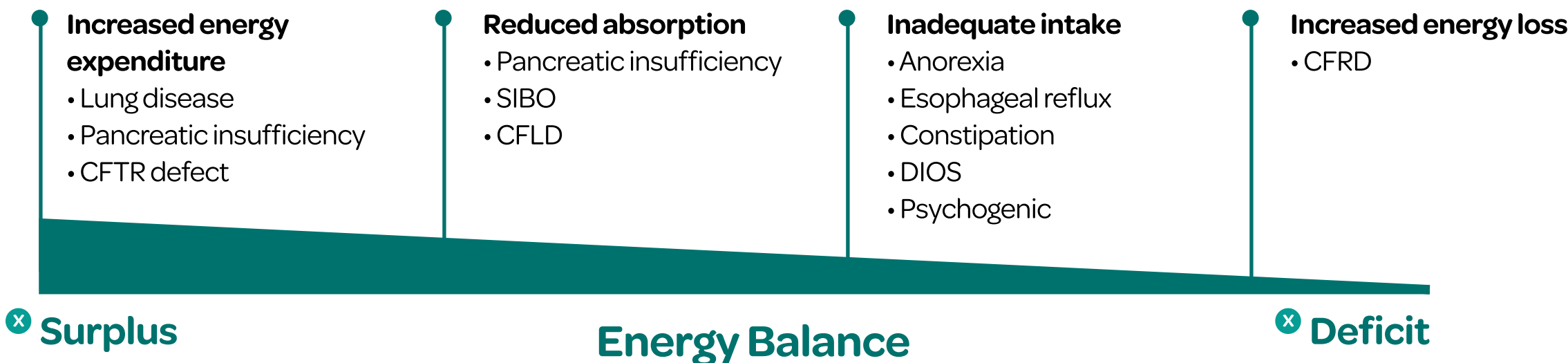
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Pathogenesis of Disordered Nutrition in CF¹⁰



- Overweight/Obese¹**
- Counsel on balanced diet
 - Increase energy expenditure with physical activity

1. Solomon M. Nutritional Issues in Cystic Fibrosis. *Clin Chest Med.* 2016;37(1):97-107.

- Underweight/Malnourished¹**
- Evaluate PERT use
 - Assess for vitamin deficiencies
 - Screen for
 - Underrecognized lung disease
 - CFRD
 - SIBO
 - Celiac disease

- Diet assessment and counseling
- Promote high calorie oral diet
- Implement behavioral modifications
- Consider oral supplements

Consider appetite stimulants

Enteral nutrition

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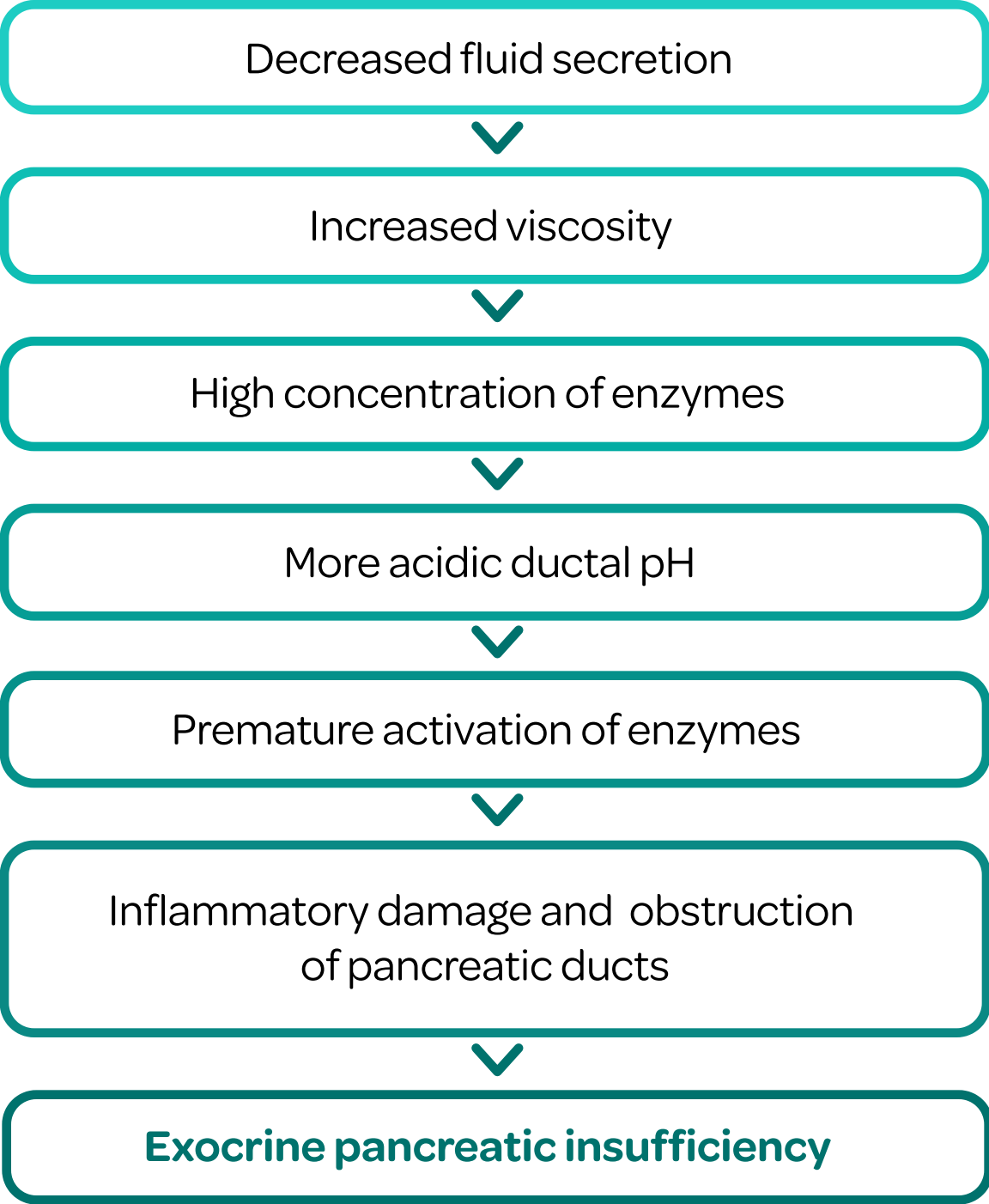
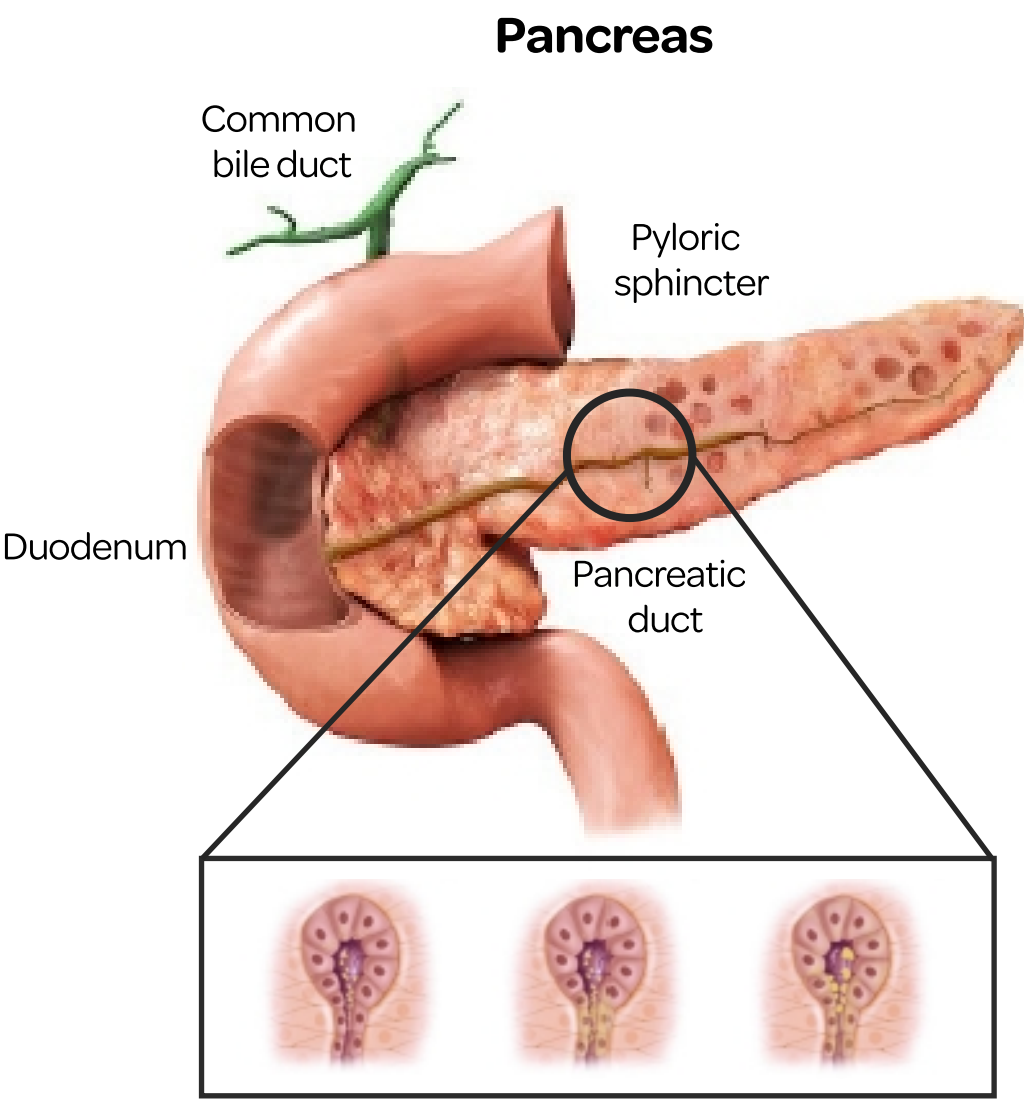
EPI in Cystic Fibrosis

Vitamin/ Mineral	Deficiency
Vitamin A	Night blindness
Vitamin D	Osteopenia/ osteoporosis
Vitamin E	Hemolytic anemia, peripheral neuropathy
Vitamin K	Coagulopathy
Calcium	Osteopenia/osteoporosis, fracture
Zinc	Loss of taste, failure to thrive
Essential Fatty Acids	Alopecia, skin rashes, easy bruising, increased infections, and poor growth

Low bone density | Unintended weight loss | Failure to reach nutritional and growth goals

EPI is present in up to 90% of patients with CF¹

Mechanism of Exocrine Pancreatic Insufficiency¹¹⁻¹⁶



Consequences of Malabsorption^{9,10,17}

- Malabsorption may lead to malnutrition
- Low levels of fat-soluble vitamins, macronutrients, and essential fatty acids

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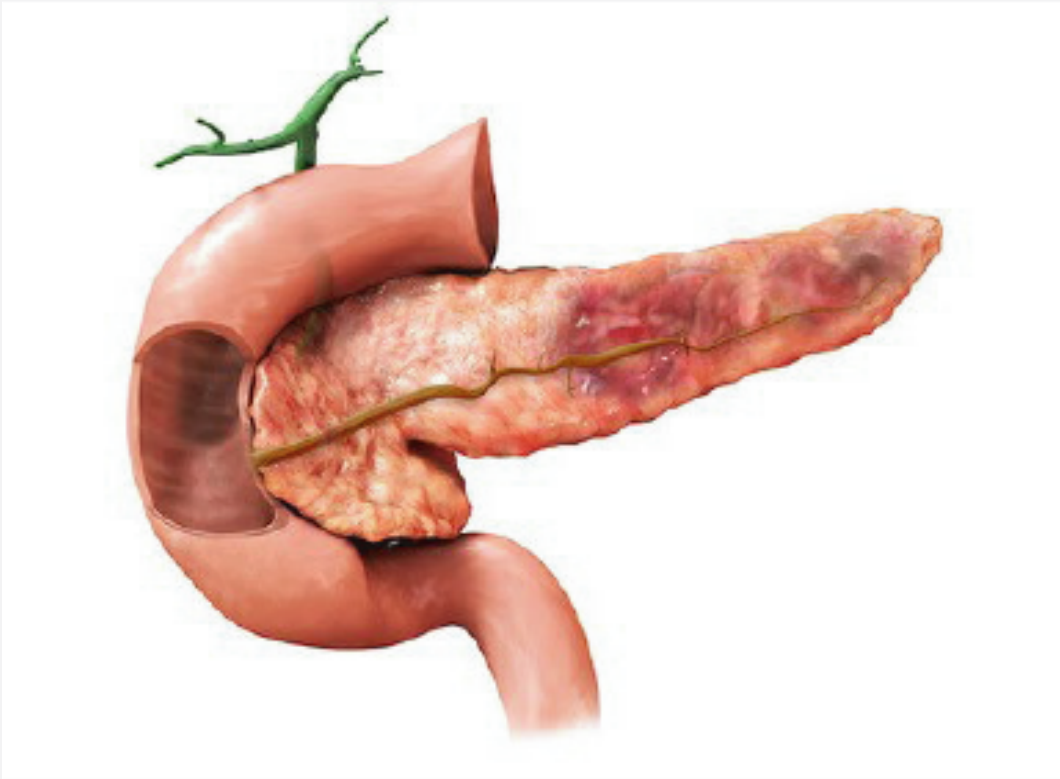
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Chronic Pancreatitis

Chronic pancreatitis is a pathologic fibroinflammatory syndrome of the pancreas in individuals with genetic, environmental, and/or other risk factors who develop persistent pathologic responses to parenchymal injury or stress.¹



Adapted from: Lindkvist B. Diagnosis and treatment of pancreatic exocrine insufficiency. *World J Gastroenterol.* 2013;19(42):7258-7266.

EPI in Chronic Pancreatitis

Reduction in Pancreatic Enzyme Quantity and/or Activity Causes EPI

EPI occurs when there is a reduction in pancreatic enzyme quantity and/or activity to a level below the threshold required to maintain normal digestion²



Destruction of pancreatic parenchyma³
Decrease in production of pancreatic enzymes



Obstruction of the pancreatic duct³
Decrease in delivery of pancreatic enzymes and bicarbonate

Incidence of EPI Increases With Duration of Chronic Pancreatitis

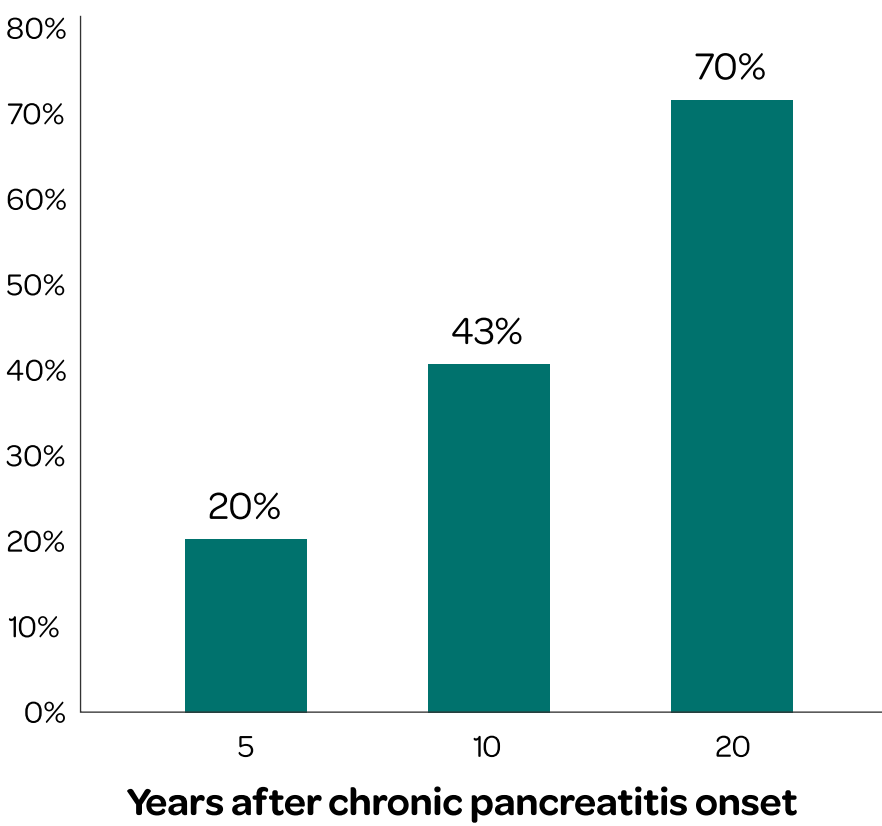
Percentage of Chronic Pancreatitis Patients With EPI³



Alcohol Use Is a Risk Factor for EPI

- Patients with chronic pancreatitis due to alcohol use have a higher cumulative incidence of EPI³

Percentage of Patients Who Develop EPI³



Pancreatectomy

GI Complications Are Frequent After Pancreatectomy

GI Complications

- Exocrine pancreatic insufficiency^{1,3,4}
- Dumping syndrome²
- Delayed gastric emptying²
- Malnutrition⁵
- Small intestinal bacterial overgrowth⁶

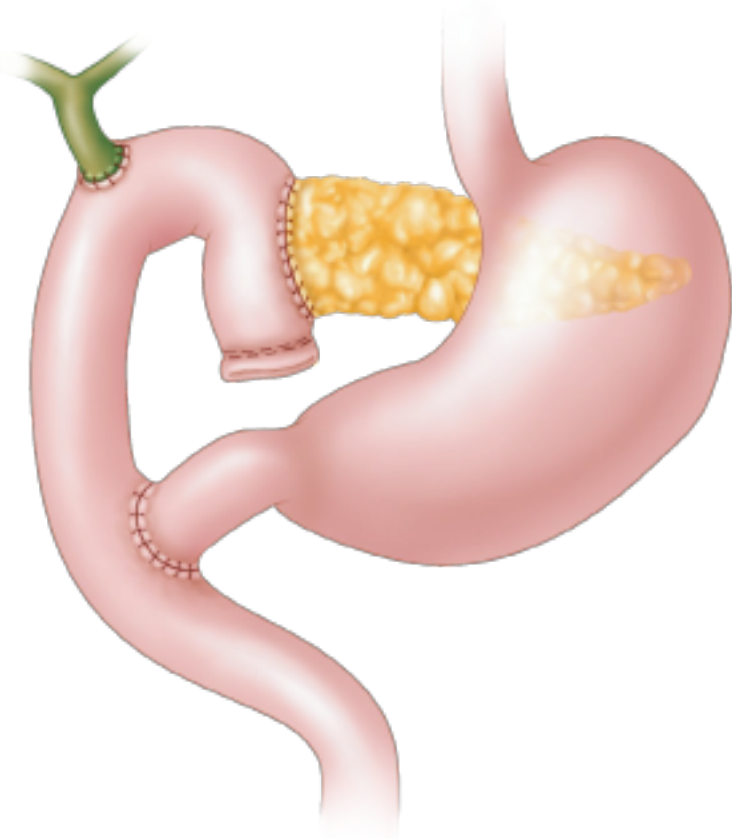
Other complications can include fatty liver, diabetes, and bone disease⁷

EPI Is a Frequent Complication of Pancreatectomy

Post-surgical Pathophysiology

EPI occurs when there is a reduction in pancreatic enzyme quantity and/or activity to a level below the threshold required to maintain normal digestion.¹

- ✓ Reduction of glandular tissue^{1,2}
- ✓ Fibrosis in the remaining pancreatic remnant^{1,2}
- ✓ Alteration of pancreatic anatomy^{1,2}
- ✓ Extensive denervation following lymph node dissection^{1,2}



1. Lindkvist B. Diagnosis and treatment of pancreatic exocrine insufficiency. *World J Gastroenterol*. 2013;19(42):7258-7266. 2. Bartel MJ, Asbun H, Stauffer J, Raimondo M. Pancreatic exocrine insufficiency in pancreatic cancer: a review of the literature. *Dig Liver Dis*. 2015;47(12):1013-1020.

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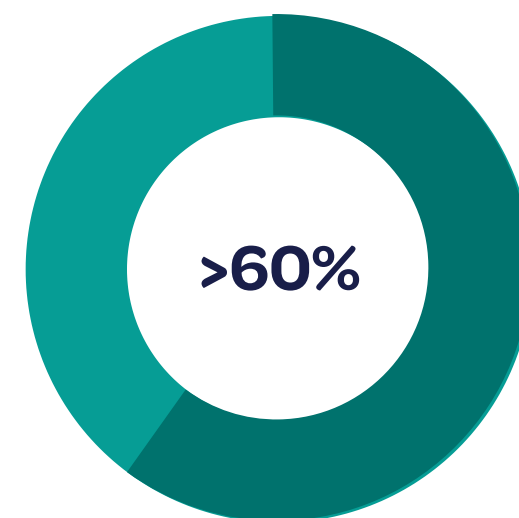
- Exocrine pancreatic insufficiency^{1,3,4}
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EPI Is a Frequent Complication of Pancreatectomy

Types of Pancreatic Surgery

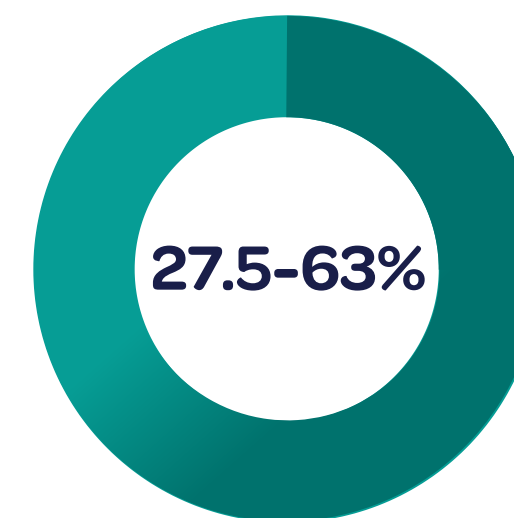
Pancreatoduodenectomy



Most studies show that **>60%**
(range: 35-100%) of patients with
chronic pancreatitis **develop**
EPI after the procedure¹

- In malignant states, the incidence
of EPI increases to 64-100%¹

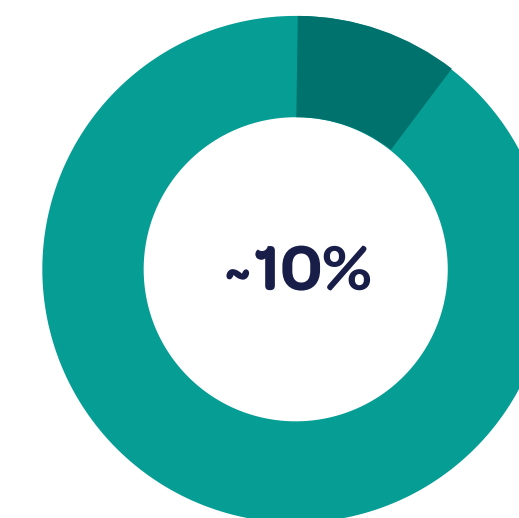
Distal pancreatectomy



EPI develops in 27.5-63%
of patients with chronic
pancreatitis **after the procedure¹**

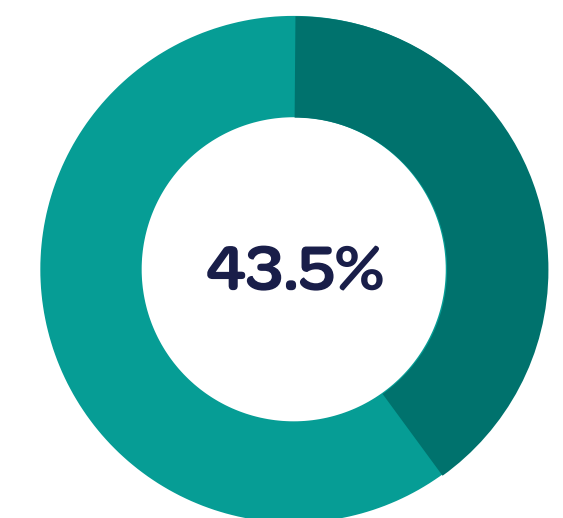
- In malignant states, the incidence
of EPI ranges from 0-42%¹

Central pancreatectomy



Rates of **EPI after the**
procedure are **~10%¹**

Total pancreatectomy



EPI symptoms were experienced
in **43.5%** of patients who have
had a total pancreatectomy²

1. Sabater L, Ausania F, Bakker OJ, et al. Evidence-based guidelines for the management of exocrine pancreatic insufficiency after pancreatic surgery. *Ann Surg*. 2016;264(6):949-958. 2. Scholten L, Stoop TF, Del Chiaro M, et al. Systematic review of functional outcome and quality of life after total pancreatectomy. *Br J Surg*. 2019;106(13):1735-1746.

EPI=exocrine pancreatic insufficiency. GI=gastrointestinal.

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Pancreatectomy

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- Dumping syndrome²
- Delayed gastric emptying²
- Malnutrition⁵
- Small intestinal bacterial overgrowth⁶

Other complications can include fatty liver, diabetes, and bone disease⁷

EPI Is a Frequent Complication of Pancreatectomy

Clinical Considerations for Post-surgical EPI

The Frequency and Severity of EPI Post-surgery Depends On:

- Type of surgery (eg, partial resection or reconstruction vs total pancreatectomy)¹⁻⁴
- Quantity and quality of the remaining pancreatic tissue¹⁻⁴
- Resection of parts of stomach and duodenum^{1,2}
 - Changes in gut pH and delayed gastric emptying^{1,2}
- Ductal obstruction of the pancreatic anastomosis^{1,2}
- Formation of a pancreaticojejunostomy and hepaticojejunostomy on a Roux loop³
 - Potential asynchrony in the delivery of pancreatic secretions and bile³
- Timing of exocrine function assessment³
- Test used in assessment of exocrine function³



International Study Group in Pancreatic Surgery (ISGPS) Guideline

Regardless of the type of pancreatic resection or reconstruction, patients should be monitored carefully to assess for the presence of EPI.⁵

1. Sabater L, Ausania F, Bakker OJ, et al. Evidence-based guidelines for the management of exocrine pancreatic insufficiency after pancreatic surgery. *Ann Surg.* 2016;264(6):949-958. 2. Lim PW, Dinh KH, Sullivan M, et al. Thirty-day outcomes underestimate endocrine and exocrine insufficiency after pancreatic resection. *HPB (Oxford).* 2016;18(4):360-366. 3. Phillips ME. Pancreatic exocrine insufficiency following pancreatic resection. *Pancreatology.* 2015;15(5):449-455. 4. Bartel MJ, Asbun H, Stauffer J, Raimondo M. Pancreatic exocrine insufficiency in pancreatic cancer: a review of the literature. *Dig Liver Dis.* 2015;47(12):1013-1020. 5. Gianotti L, Besselink MG, Sandini M, et al. Nutritional support and therapy in pancreatic surgery: a position paper of the International Study Group on Pancreatic Surgery (ISGPS). *Surgery.* 2018;164(5):1035-1048.

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- Exocrine pancreatic insufficiency^{1,3,4}
- Dumping syndrome²
- Delayed gastric emptying²
- Malnutrition⁵
- Small intestinal bacterial overgrowth⁶

Other complications can include fatty liver, diabetes, and bone disease⁷

EPI Is a Frequent Complication of Pancreatectomy

Nutritional Consequences of EPI



Unintentional weight loss¹



Fat-soluble vitamin deficiencies, including vitamins A, D, E, and K^{2,3}



Malnutrition resulting from nutrient deficiency and fat malabsorption¹



Consequences for poor outcomes
(eg, length of hospital stay, fistula, survival)⁴



Overt symptoms of EPI may be preceded by clinically relevant nutrient deficiencies.¹

1. Lindkvist B. Diagnosis and treatment of pancreatic exocrine insufficiency. *World J Gastroenterol*. 2013;19(42):7258-7266. 2. Sikkens EC, Cahen DL, Koch AD, et al. The prevalence of fat-soluble vitamin deficiencies and a decreased bone mass in patients with chronic pancreatitis. *Pancreatol*. 2013;13(3):238-242. 3. Lindkvist B, Phillips ME, Domínguez-Muñoz JE. Clinical, anthropometric and laboratory nutritional markers of pancreatic exocrine insufficiency: prevalence and diagnostic use. *Pancreatol*. 2015;15(6):589-597. 4. Othman MO, Harb D, Barkin JA. Introduction and practical approach to exocrine pancreatic insufficiency for the practicing clinician. *Int J Clin Pract*. 2018;72(2):e13066.

EPI=exocrine pancreatic insufficiency. GI=gastrointestinal.

1. Berry AJ. Pancreatic surgery: indications, complications, and implications for nutrition intervention. *Nutr Clin Pract*. 2013;28(3):330-357. 2. Pappas S, Krzywda E, McDowell N. Nutrition and pancreaticoduodenectomy. *Nutr Clin Pract*. 2010;25(3):234-243. 3. Lindkvist B. Diagnosis and treatment of pancreatic exocrine insufficiency. *World J Gastroenterol*. 2013;19(42):7258-7266. 4. Pezzilli R, Andriulli A, Bassi C, et al. Exocrine pancreatic insufficiency in adults: a shared position statement of the Italian Association for the Study of the Pancreas. *World J Gastroenterol*. 2013;19(44):7930-7946. 5. Decher N, Berry A. Post-Whipple: a practical approach to nutrition management. *Pract Gastroenterol*. 2012;36(8):30-42. 6. Muniz CK, dos Santos JS, Pfrimer K, et al. Nutritional status, fecal elastase-1, and 13C-labeled mixed triglyceride breath test in the long-term after pancreaticoduodenectomy. *Pancreas*. 2014;43(3):445-450. 7. Petzel MQB, Hoffman L. Nutrition implications for long-term survivors of pancreatic cancer surgery. *Nutr Clin Pract*. 2017;32(5):588-598.

Causes of EPI

Physiology and Prevalence

Causes of EPI

Symptoms and Diagnosis

Burden

Treatment

Treatment Insights

Pancreatectomy

GI Complications Are Frequent After Pancreatectomy

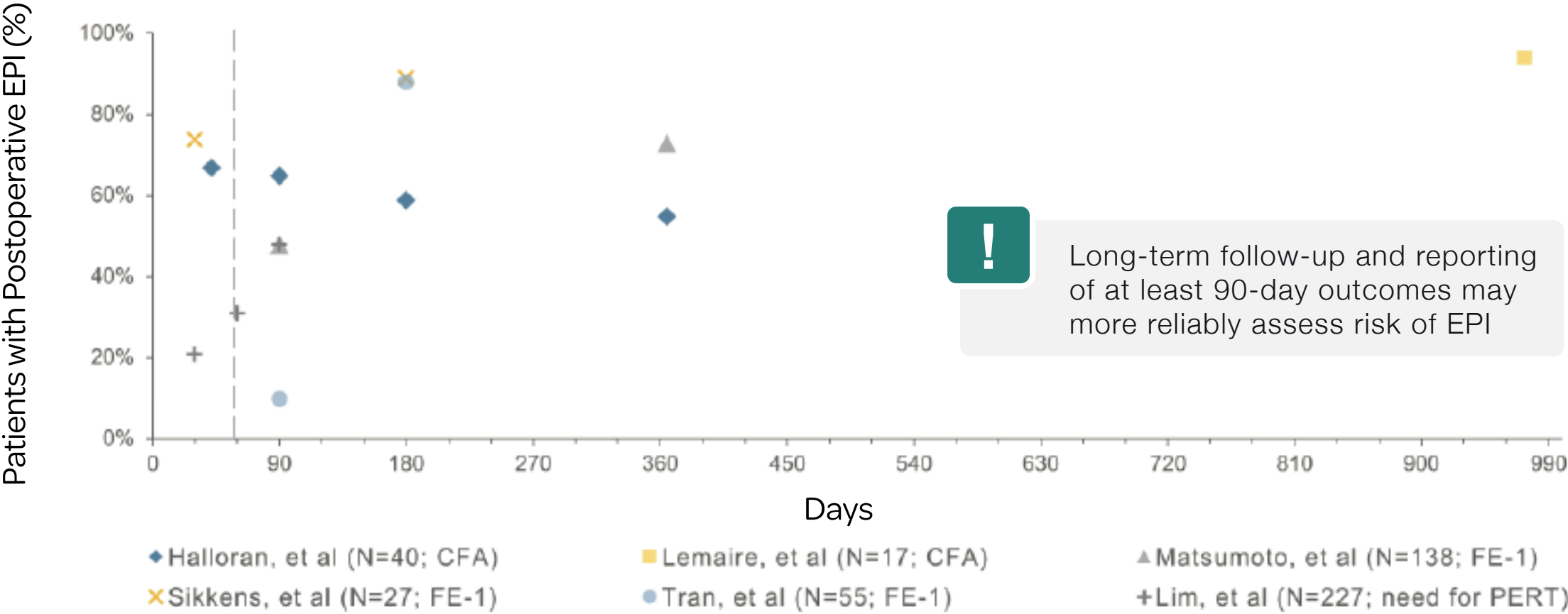
GI Complications

- Exocrine pancreatic insufficiency^{1,3,4}
- Dumping syndrome²
- Delayed gastric emptying²
- Malnutrition⁵
- Small intestinal bacterial overgrowth⁶

Other complications can include fatty liver, diabetes, and bone disease⁷

EPI Is a Frequent Complication of Pancreatectomy

Timing of EPI Assessment & Onset¹⁻⁶



FE-1=fecal elastase 1. CFA=coefficient of fat absorption. PERT=pancreatic enzyme replacement therapy.
1. Lim PW, Dinh KH, Sullivan M, et al. Thirty-day outcomes underestimate endocrine and exocrine insufficiency after pancreatic resection. *HPB (Oxford)*. 2016;18(4):360-366. 2. Halloran CM, Cox TF, Chauhan S, et al. Partial pancreatic resection for pancreatic malignancy is associated with sustained pancreatic exocrine failure and reduced quality of life: a prospective study. *Pancreatol*. 2011;11(6):535-545. 3. Lemaire E, O'Toole D, Sauvanet A, Hammel P, Belghiti J, Ruszniewski P. Functional and morphological changes in the pancreatic remnant following pancreaticoduodenectomy with pancreaticogastric anastomosis. *Br J Surg*. 2000;87(4):434-438. 4. Matsumoto J, Traverso LW. Exocrine function following the Whipple operation as assessed by stool elastase. *J Gastrointest Surg*. 2006;10(9):1225-1229. 5. Sikkens EC, Cahen DL, de Wit J, Looman CW, van Eijck C, Bruno MJ. Prospective assessment of the influence of pancreatic cancer resection on exocrine pancreatic function. *Br J Surg*. 2014;101(2):109-113. 6. Tran TC, van 't Hof G, Kazemier G, et al. Pancreatic fibrosis correlates with exocrine pancreatic insufficiency after pancreatoduodenectomy. *Dig Surg*. 2008;25(4):311-318.

Causes of EPI

Physiology and
Prevalence

Causes of EPI

Symptoms
and Diagnosis

Burden

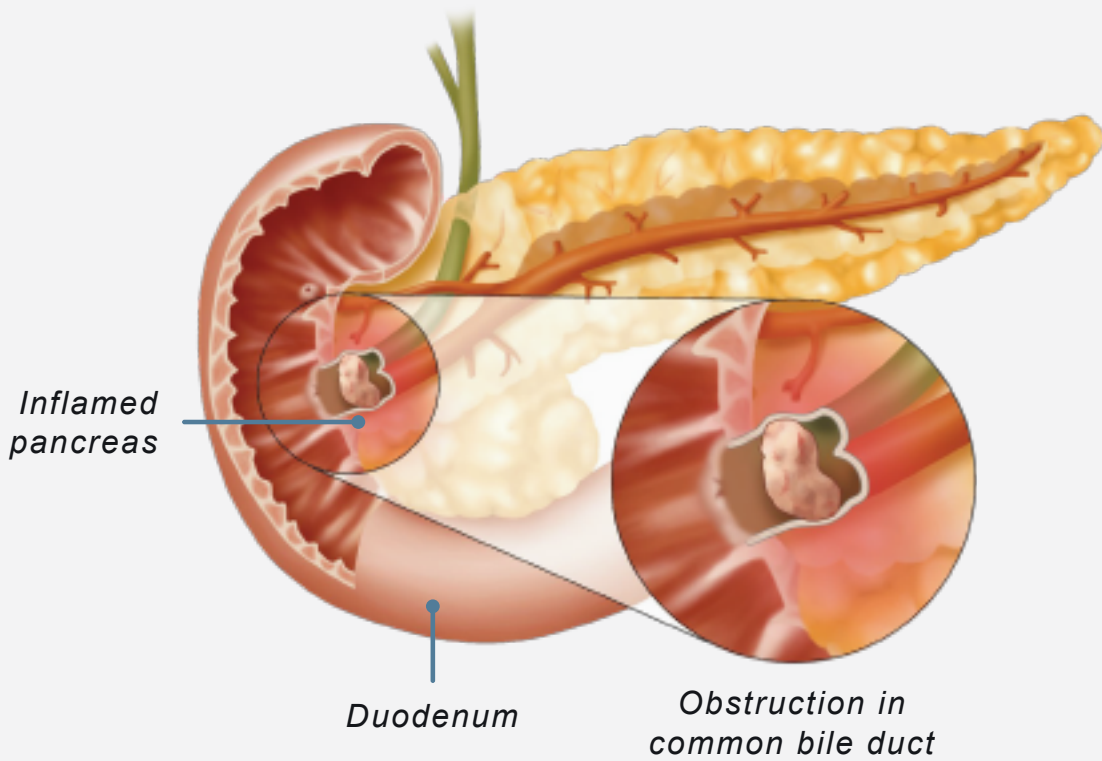
Treatment

Treatment
Insights

Acute Pancreatitis¹⁻⁴

Etiology of Acute Pancreatitis

- Acute pancreatitis is frequently caused by
 - Obstruction of the common bile duct by stones¹
 - Alcohol abuse¹
- Characterized by acute inflammation of the pancreas²
 - Pancreatic necrosis occurs in ~20% of patients³



Incidence of Acute Pancreatitis



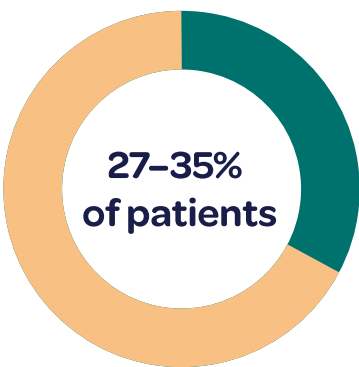
10–44 cases per 100,000
people every year⁴

EPI in Acute Pancreatitis^{3,5,6}

Multiple Potential Mechanisms Can Lead to EPI in Acute Pancreatitis³

- Ductal obstruction due to inflammation
- Secondary impairment of hormonal mediators
- Damaged receptors controlling enzyme-releasing acinar cells
- Diminished pancreatic function following necrosis or surgical removal of necrosis

EPI Has Increased Prevalence in Moderate or Severe Acute Pancreatitis^{3,5}



- High heterogeneity exists between individual studies^{3,5}
- Higher prevalence in patients with moderate or severe acute pancreatitis attack (27–30%) compared with mild acute pancreatitis attack (16%)³

Risk of EPI in Acute Pancreatitis^{3,5,6}

- Recurrence of acute pancreatitis
- Acute pancreatitis severity
- Extent of necrosis
- Alcoholic etiology
- Necrosectomy

Causes of EPI

Physiology and
Prevalence

Causes of EPI

Symptoms
and Diagnosis

Burden

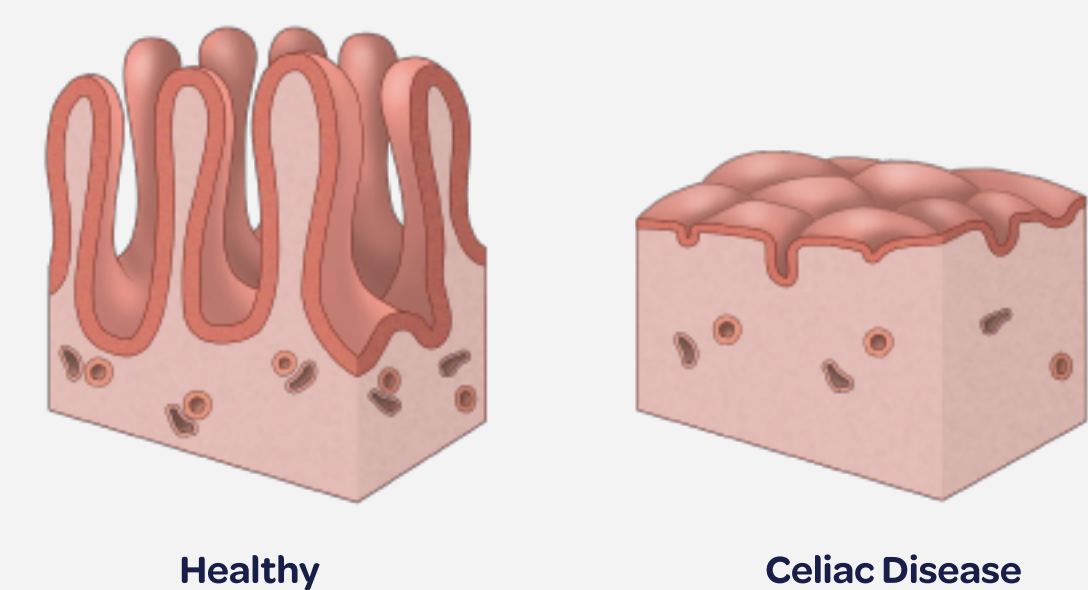
Treatment

Treatment
Insights

Celiac Disease¹⁻⁴

Etiology of Celiac Disease^{1,2}

- T-cell-mediated reaction to gluten that causes inflammatory injury to the villi of the small intestine and results in malabsorption¹
- Changes may be present in both the endocrine and exocrine functions of the pancreas²
- Gluten-free diet is essential¹



The small intestine villi of a celiac patient (pictured on the right) are damaged, resulting in malabsorption.

Prevalence of Celiac Disease^{3,4}



~1% in the United States and Europe

EPI in Celiac Disease⁵⁻¹¹

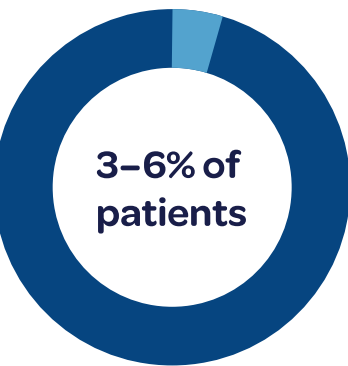
Potential Mechanisms of EPI in Celiac Disease

- Untreated celiac disease is associated with impaired intestinal hormonal stimulation of the pancreas⁵
 - Impaired synthesis, storage, and release of secretagogues (ie, CCK and secretin)⁶
 - Defective postprandial response (CCK stimulation) due to intestinal inflammation and mucosal villous atrophy^{6,7}
- Substantially impaired exocrine pancreatic function might be caused by comorbid chronic pancreatitis⁶
- Protein malnutrition, potentially due to untreated malabsorption, is associated with decreased pancreatic enzyme secretion and pancreatic structural changes⁶

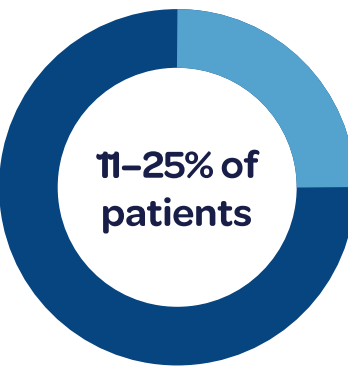
Patients With Celiac Disease May Develop EPI

Prevalence of EPI in Patients With Celiac Disease⁷⁻¹¹

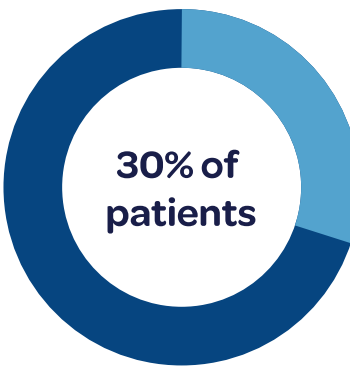
- Resolves with a gluten-free diet in most patients



who are on a
gluten-free diet
have EPI^{9,10}



with untreated
celiac disease
have EPI^{9,10}



with celiac disease not
responding to gluten-free
diet have EPI⁹



According to ACG clinical guidelines, cases of non-responsive celiac disease should be assessed for EPI.¹¹

EPI=exocrine pancreatic insufficiency. CCK=cholecystokinin. ACG=American College of Gastroenterology.
1. Husby S, Koletzko S, Korponay-Szabó IR, et al. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. *J Pediatr Gastroenterol Nutr.* 2012;54(1):136-160. 2. Freeman HJ. Pancreatic endocrine and exocrine changes in celiac disease. *World J Gastroenterol.* 2007;13(47):6344-6346. 3. Ludvigsson JF, Montgomery SM, Ekbom A. Risk of pancreatitis in 14,000 individuals with celiac disease. *Clin Gastroenterol Hepatol.* 2007;5(11):1347-1353. 4. Evans KE, Leeds JS, Morley S, Sanders DS. Pancreatic insufficiency in adult celiac disease: do patients require long-term enzyme supplementation? *Dig Dis Sci.* 2010;55(10):2999-3004. 5. Pezzilli R, Andriulli A, Bassi C, et al. Exocrine pancreatic insufficiency in adults: a shared position statement of the Italian Association for the Study of the Pancreas. *World J Gastroenterol.* 2013;19(44):7930-7946. 6. Singh VK, Haupt ME, Geller DE, Hall JA, Quintana Diez PM. Less common etiologies of exocrine pancreatic insufficiency. *World J Gastroenterol.* 2017;23(39):7059-7076. 7. Capurso G, Traini M, Piciocchi M, Signoretti M, Arcidiacono PG. Exocrine pancreatic insufficiency: prevalence, diagnosis, and management. *Clin Exp Gastroenterol.* 2019;12:129-139. 8. Rana S, Dambalkar A, Chhabra P, Sharma R, Nada R, Sharma V, Rana S, Bhasin D. Is pancreatic exocrine in celiac disease related to structural alterations in pancreatic parenchyma? *Ann Gastroenterol.* 2016;29(3):363-366. 9. Leeds JS, Hopper AD, Hurlstone DP, Edwards SJ, McAlindon ME, Lobo AJ, Donnelly MT, Morley S, Sanders DS. Is exocrine pancreatic insufficiency in adult coeliac disease a cause of persisting symptoms? *Aliment Pharmacol Ther.* 2007;25(3):265-71. 10. Vujasinovic M, Tepes B, Volfand J, Rudolf S. Exocrine pancreatic insufficiency. MRI of the pancreas and serum nutritional markers in patients with coeliac disease. *Postgrad Med J.* 2015;91(1079):497-500. 11. Rubio-Tapia A, Hill I, Kelly C, Calderwood A, Murray J. ACG Clinical Guidelines: Diagnosis and Management of Celiac Disease. *Am J Gastroenterol.* 2013;108(5):656-676.

Causes of EPI

Physiology and
Prevalence

Causes of EPI

Symptoms
and Diagnosis

Burden

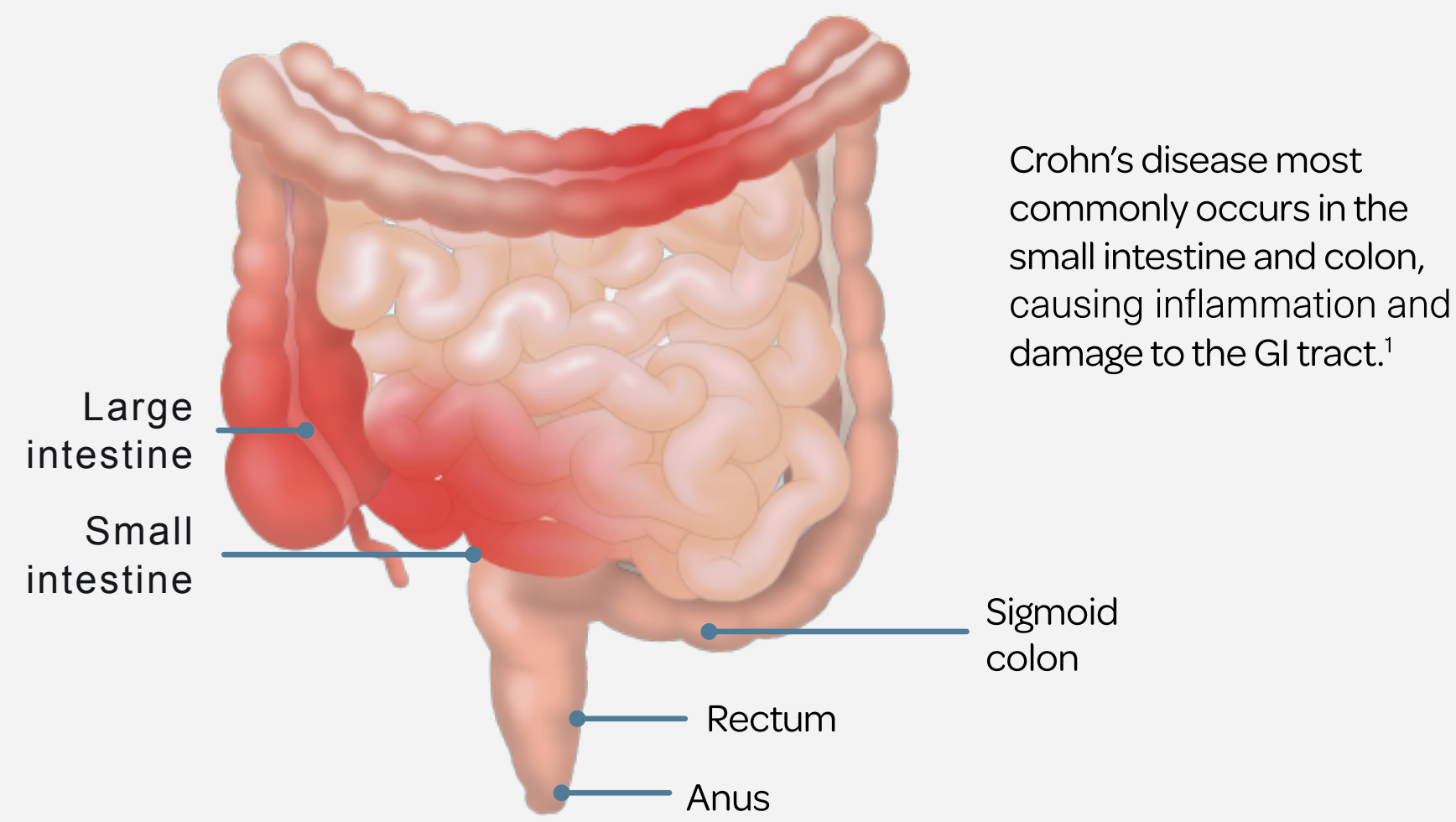
Treatment

Treatment
Insights

Crohn's Disease¹⁻²

Etiology of Crohn's Disease

- Crohn's disease causes chronic inflammation and damage to the GI tract¹



Incidence of Crohn's Disease²



Crohn's disease may affect as many as 780,000 people in the United States

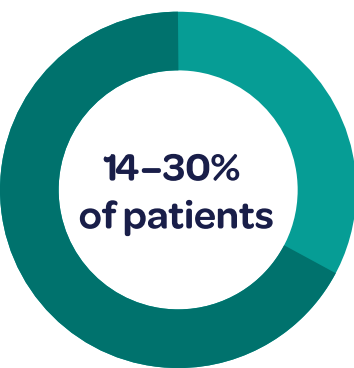
EPI in Crohn's Disease³⁻⁴

Potential Mechanisms of EPI in Crohn's Disease³⁻⁴

- Underlying pancreatitis
 - Pancreatic autoantibodies (present in ~1/3 of patients)
 - IBD treatments (eg, thiopurines, aminosalicylates, corticosteroids, intralipids) can cause pancreatitis
- Duodenal reflux due to inflammation may damage the pancreatic duct
- Reduced intestinal hormone secretion due to scarring/inflammation, which insufficiently stimulates the pancreas

Patients With Crohn's Disease May Develop EPI

Prevalence of EPI in Crohn's Disease³



Patients at Increased Risk of Developing EPI if Experiencing³:

- ≥3 bowel movements per day
- Loose stools
- History of surgery

Causes of EPI

Physiology and
Prevalence

Causes of EPI

Symptoms
and Diagnosis

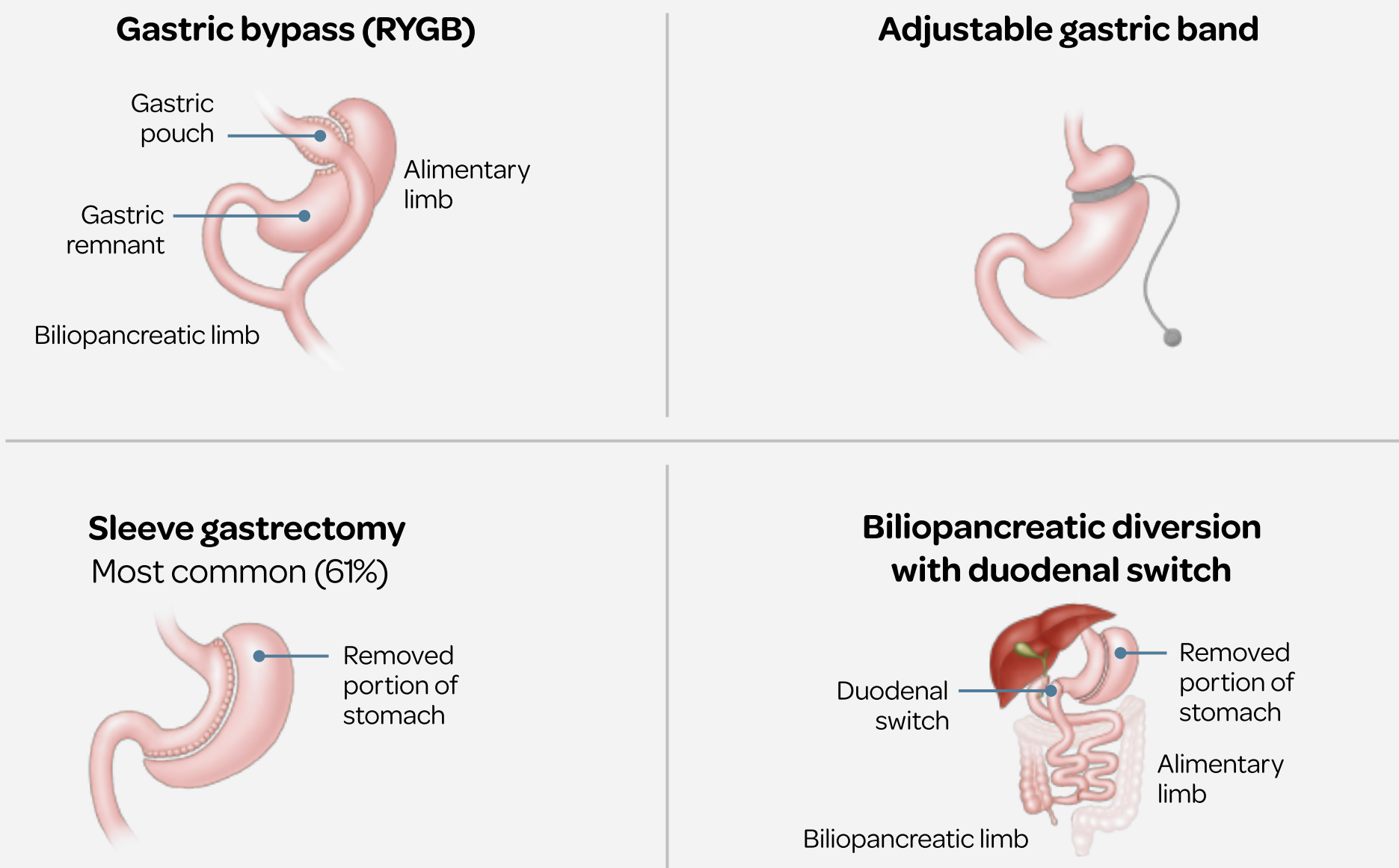
Burden

Treatment

Treatment
Insights

Gastric Surgery¹⁻³

Common Bariatric Procedures^{1,2}



- Obesity affects 42.4% of the adult population in the United States³
- From 2011–2018, there was a 59% increase in bariatric surgeries in the United States¹
 - 252,000 surgeries in 2018¹

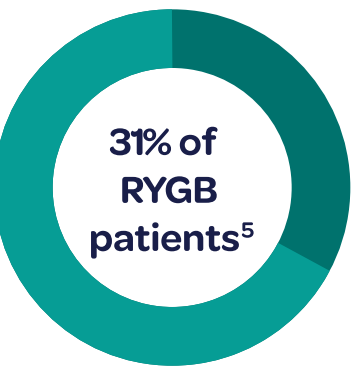
EPI in Gastric Surgery⁴⁻⁷

Multiple Potential Mechanisms Can Lead To EPI in Gastric Surgery⁴

- Altered gastric relaxation due to the absence of neural gastric reflexes
- Absence of neural gastric stimulation responsible for pancreatic secretion
- Rapid gastric emptying and asynchrony between gastric emptying and biliopancreatic secretion
- Extensive denervation of the pancreas due to lymph node dissection and truncal vagotomy

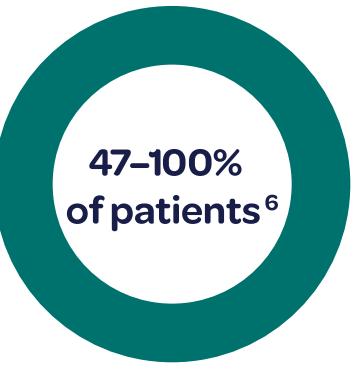
Patients Who Have Undergone Gastric Surgery May Develop EPI⁵⁻⁷

Prevalence of EPI in Bariatric Surgery



- Sleeve gastrectomy: some EPI expected, but there is a lack of robust clinical studies²
- Gastric banding: low likelihood of EPI²

Rate of EPI in Gastric Surgery



- Exact incidence unknown⁶
- Greater incidence in patients with total gastrectomy, duodenal bypass procedures, and vagal denervation^{6,7}

*Median age, 49 years; mean presurgical weight, 131.1 kg; female (92.3%).
EPI=exocrine pancreatic insufficiency. RYGB=Roux-en-Y Gastric Bypass.
1. Estimate of bariatric surgery numbers, 2011–2018. American Society for Metabolic and Bariatric Surgery. Accessed September 21, 2020. 2. Vujasinovic M, Valente R, Thorell A, et al. Pancreatic exocrine insufficiency after bariatric surgery. *Nutrients*. 2017;9(11):1241. 3. Hales CM, Carroll DM, Fryar CD, Ogden CL. Prevalence of obesity and severe obesity among adults: United States, 2017–2018. National Center for Health Statistics. Published 2020. Accessed September 21, 2020. 4. Antonini F, Crippa S, Falconi M, Macarri G, Pezzilli R. Pancreatic enzyme replacement therapy after gastric resection: an update. *Dig Liver Dis*. 2018;50(1):1–5. 5. Borbély Y, Plebani A, Kröll D, Ghisla S, Nett PC. Exocrine pancreatic insufficiency after Roux-en-Y gastric bypass. *Surg Obes Relat Dis*. 2016;12(4):790–794. 6. Lee AHH, Ward SM. Pancreatic exocrine insufficiency after total gastrectomy - a systematic review. *J Pancreas*. 2019;20(5):130–137. 7. Capurso G, Traini M, Piciocchi M, Signoretti M, Arcidiacono PG. Exocrine pancreatic insufficiency: prevalence, diagnosis, and management. *Clin Exp Gastroenterol*. 2019;12:129–139. 8. O’Keefe SJD, Rakitt T, Ou J, et al. Pancreatic and intestinal function post Roux-en-Y gastric bypass surgery for obesity. *Clin Transl Gastroenterol*. 2017;8(8):e112.

Pancreatic Cancer¹

Modifiable Risk Factors for Pancreatic Cancer¹

- Tobacco use
- Obesity
- Diabetes
- Chronic pancreatitis

Unmodifiable Risk Factors for Pancreatic Cancer¹

- Age
- Gender
- Race
- Family history
- Inherited genetic syndromes (eg, hereditary breast cancer, familial pancreatitis)

Incidence of Pancreatic Cancer²



- In 2022, it is estimated that there will be 62,210 new cases of pancreatic cancer in the United States
- Currently the third leading cause of cancer-related death

EPI in Pancreatic Cancer³⁻¹¹

Multiple Potential Mechanisms Can Lead to EPI in Pancreatic Cancer³⁻⁶

- In resectable pancreatic cancer, degree of EPI following pancreatic resection is influenced by multiple factors, such as
 - Type of surgery³
 - Extent of remaining tissue⁴
- Unresectable pancreatic cancer
 - Pancreatic duct obstruction³
 - Pancreatic atrophy secondary to duct obstruction and fibrosis³⁻⁵
 - Ongoing destruction of pancreatic parenchyma by the tumor^{3,6}

EPI Contributes to the Multifactorial Weight Loss in Patients With Pancreatic Cancer⁷⁻¹⁰

- At diagnosis of pancreatic ductal adenocarcinoma, 71.5% of patients had >5% weight loss⁷

Patients With Pancreatic Cancer May Develop EPI

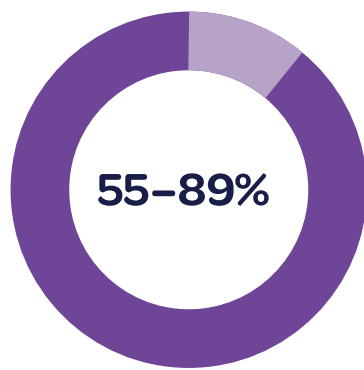
Prevalence of EPI in Pancreatic Cancer^{6,11-13}

Unresectable
Pancreatic Cancer^{6,11}



of patients with unresectable pancreatic cancer have EPI

Resectable
Pancreatic Cancer^{12,13}



of patients have EPI after pancreatic surgery

EPI=exocrine pancreatic insufficiency.

1. American Cancer Society. Pancreatic Cancer Risk Factors. Accessed April 28, 2022. <https://www.cancer.org/cancer/pancreatic-cancer/causes-risks-prevention/risk-factors.html> 2. Cancer Stat Facts: Pancreatic Cancer. National Cancer Institute. Accessed April 25, 2022. <https://seer.cancer.gov/statfacts/html/pancreas.html> 3. Papadoniou N, Kosmas C, Gennatas K, et al. Prognostic factors in patients with locally advanced (unresectable) or metastatic pancreatic adenocarcinoma: a retrospective analysis. *Anticancer Res.* 2008;28(1B):543-549. 4. Bartel MJ, Asbun H, Stauffer J, Raimondo M. Pancreatic exocrine insufficiency in pancreatic cancer: a review of the literature. *Dig Liver Dis.* 2015;47(12):1013-1020. 5. Phillips ME. Pancreatic exocrine insufficiency following pancreatic resection. *Pancreatol.* 2015;15(5):449-455. 6. Partelli S, Frulloni L, Minniti C, et al. Faecal elastase-1 is an independent predictor of survival in advanced pancreatic cancer. *Dig Liver Dis.* 2012;44(11):945-951. 7. Nemer L, Krishna SG, Shah ZK, et al. Predictors of Pancreatic Cancer-Associated Weight Loss and Nutritional Interventions. *Pancreas.* 2017;46(9):1152-1157. 8. Van Cutsem E, Arends J. The causes and consequences of cancer-associated malnutrition. *Eur J Oncol Nurs.* 2005;9 (suppl 2):S51-S63. 9. Ronga I, Gallucci F, Riccardi F, Uomo G. Anorexia-cachexia syndrome in pancreatic cancer: recent advances and new pharmacological approach. *Adv Med Sci.* 2014;59(1):1-6. 10. Mueller TC, Burmeister MA, Bachmann J, Martignoni ME. Cachexia and pancreatic cancer: are there treatment options?. *World J Gastroenterol.* 2014;20(28):9361-9373. 11. Sikkens EC, Cahen DL, de Wit J, Looman CWN, van Eijck C, Bruno MJ. A prospective assessment of the natural course of the exocrine pancreatic function in patients with a pancreatic head tumor. *J Clin Gastroenterol.* 2014;48(5):e43-e46. 12. Belyaev O, Herzog T, Chromik AM, Meurer K, Uhl W. Early and late postoperative changes in the quality of life after pancreatic surgery. *Langenbecks Arch Surg.* 2013;398(4):547-555. 13. Lim JH, Park JS, Yoon DS. Preoperative fecal elastase-1 is a useful prognostic marker following curative resection of pancreatic cancer. *HPB (Oxford).* 2017;19(5):388-395.

Causes of EPI

Physiology and
Prevalence

Causes of EPI

Symptoms
and Diagnosis

Burden

Treatment

Treatment
Insights

Type 1 Diabetes

Etiology of Type 1 Diabetes

- Typically has an early onset¹
- An autoimmune disease characterized by immune-mediated destruction of islet cells, leading to a loss of insulin production

Prevalence of Type 1 Diabetes



In 2018, ~1.6 million people in the United States had T1DM²

- Includes ~187,000 children and adolescents

EPI in Type 1 Diabetes^{1,3,4}

Potential Mechanisms of Pancreatic Damage in Patients With Diabetes

- The exact mechanism of exocrine dysfunction in T1DM is unclear¹
- Impaired acinar-islet interaction with imbalances in endocrine stimulation³
- Diminished trophic effects of insulin, resulting in pancreatic atrophy and fibrosis³
- Autonomic diabetic neuropathy and diabetic microangiopathy^{1,3}
- Presence of autoantibodies against exocrine tissue³

Patients With Type 1 Diabetes May Develop EPI

Prevalence of EPI in Type 1 Diabetes

- EPI in diabetes has been recognized, but the prevalence is not well-characterized^{3,4}
- Heterogeneity may be due to variability in specificity and types of measurements for pancreatic function⁴

Symptoms and Diagnosis

Physiology and Prevalence

Causes of EPI

Symptoms and Diagnosis

Burden

Treatment

Treatment Insights

There Is No Single Convenient and Specific Diagnostic Test for EPI¹⁻³

Test ¹	Description ¹	Limitations ¹
Direct pancreatic function	<ul style="list-style-type: none">Peak bicarbonate concentration following secretin stimulationCutoff suggestive of EPI: <80 mEq/L over 60 min	<ul style="list-style-type: none">InvasiveLimited availability
Quantitative fecal fat	<ul style="list-style-type: none">Amount of fat remaining in stool compared with fat content of dietCutoff suggestive of EPI: >7 g/100 g of fat ingested	<ul style="list-style-type: none">Limited useNot specific for EPI
FE-1	<ul style="list-style-type: none">Amount of pancreatic elastase in stoolCutoff suggestive of EPI: <200 µg/g stool	<ul style="list-style-type: none">Less sensitive for mild EPIFalse positives with watery stool

Include EPI in the Differential Diagnosis Due to Overlapping Symptomatology⁴⁻¹⁴

Symptoms	EPI ⁴	IBS-D ^{5,6}	SIBO ⁷	IBD ⁸	Celiac Disease ⁹
Diarrhea					
Abdominal Pain					
Bloating					
Flatulence					

Clinical Features	EPI	IBS-D	SIBO	IBD	Celiac Disease
Symptom Onset Related to Food Intake	X ¹¹		X ⁷ Particularly foods high in sugar and fiber ¹⁰	X ¹⁰ Symptoms may occur despite fasting (ileitis) ¹⁰	X ¹⁰ Gluten dependent (or triggered by gluten), improves with fasting ¹⁰
Nocturnal Symptoms		Symptoms improve at night ¹⁰		X ¹⁰ Ileitis	
Stool Quality	Fatty ¹⁰ Stool may not be very loose ¹⁰	Watery ¹⁰	Fatty ¹⁰	Bloody/Purulent ¹⁰	Watery/Fatty ¹⁰
Urgency	X ¹³	X ⁵		X ⁸	
Fecal Incontinence		X ¹⁴		X ¹²	
Unexplained Weight Loss	X ¹¹		Only in extreme cases ⁷	X ¹⁰	X ⁹

EPI=exocrine pancreatic insufficiency. FE-1=fecal elastase 1. IBS-D=irritable bowel syndrome with diarrhea. SIBO=small intestinal bacterial overgrowth. IBD=inflammatory bowel disease.

1. Hart PA, Conwell DL. Diagnosis of exocrine pancreatic insufficiency. *Curr Treat Options Gastroenterol.* 2015;13(3):347-353. 2. Working Party of the Australasian Pancreatic Club, Smith RC, Smith SF, et al. Summary and recommendations from the Australasian guidelines for the management of pancreatic exocrine insufficiency. *Pancreatolgy.* 2016;16(2):164-180. 3. Lindkvist B. Diagnosis and treatment of pancreatic exocrine insufficiency. *World J Gastroenterol.* 2013;19(42):7258-7266. 4. Alkaade S, Vareedayah AA. A primer on exocrine pancreatic insufficiency, fat malabsorption, and fatty acid abnormalities. *Am J Manag Care.* 2017;23(12 Suppl):S203-S209. 5. Lacy BE, Pimentel M, Brenner DM, et al. ACG Clinical Guideline: Management of Irritable Bowel Syndrome. *Am J Gastroenterol.* 2021;116(1):17-44. doi:10.14309/ajg.0000000000001036 6. Owyang C. Irritable Bowel Syndrome. In: Jameson J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J. eds. *Harrison's Principles of Internal Medicine*, 20e. McGraw Hill; 2018. Accessed April 28, 2022. <https://accessmedicine.mhmedical.com/content.aspx?bookid=2129§ionid=1922826707>. 7. Pimentel M, Saad RJ, Long MD, Rao SSC. ACG Clinical Guideline: Small Intestinal Bacterial Overgrowth. *Am J Gastroenterol.* 2020;115(2):165-178. doi:10.14309/ajg.0000000000000501 8. Farrell D, McCarthy G, Savage E. Self-reported Symptom Burden in Individuals with Inflammatory Bowel Disease. *J Crohns Colitis.* 2016;10(3):315-322. doi:10.1093/ecco-jcc/jjv218 9. Rubio-Tapia A, Hill ID, Kelly CP, Calderwood AH, Murray JA; American College of Gastroenterology. ACG clinical guidelines: diagnosis and management of celiac disease. *Am J Gastroenterol.* 2013;108(5):656-677. doi:10.1038/ajg.2013.79 10. Burgers K, Lindberg B, Bevis ZJ. Chronic Diarrhea in Adults: Evaluation and Differential Diagnosis. *Am Fam Physician.* 2020;101(8):472-480. 11. Phillips ME, Hopper AD, Leeds JS, et al. Consensus for the management of pancreatic exocrine insufficiency: UK practical guidelines. *BMJ Open Gastroenterol.* 2021;8(1):e000643. doi:10.1136/bmjgast-2021-000643 12. Gu P, Kuenzig ME, Kaplan GG, Pimentel M, Rezaie A. Fecal Incontinence in Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis. *Inflamm Bowel Dis.* 2018;24(6):1280-1290. doi:10.1093/ibd/izx109 13. Johnson CD, Williamson N, Janssen-van Solingen G, et al. Psychometric evaluation of a patient-reported outcome measure in pancreatic exocrine insufficiency (PEI). *Pancreatolgy.* 2019;19(1):182-190. doi:10.1016/j.pan.2018.11.013 14. Simrén M, Palsson OS, Heymen S, Bajor A, Törnblom H, Whitehead WE. Fecal incontinence in irritable bowel syndrome: Prevalence and associated factors in Swedish and American patients. *Neurogastroenterol Motil.* 2017;29(2):10.1111/nmo.12919. doi:10.1111/nmo.12919

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Hiding in Plain Sight
Exocrine Pancreatic Insufficiency
In Pancreatic Disease

Practical Approaches for the Healthcare Professional

J. Enrique Domínguez-Muñoz, MD, PHD

Professor of Medicine
Director, Department of Gastroenterology and Hepatology
University Hospital of Santiago de Compostela, Spain



EPI in Pancreatic Diseases | Approved April 2022 ABBV-US-01186-E v1.0 | Company Confidential © 2021



Pancreatic Enzyme Replacement Therapy (PERT) Is the Standard of Care for EPI



PERT in EPI

What is the role of PERT in Exocrine Pancreatic Insufficiency (EPI)?

PERTs are pancreatic enzyme preparations consisting of pancrelipase, an extract containing multiple animal-derived enzyme classes, including lipases, proteases, and amylases.¹ PERT is the cornerstone of treatment for EPI.²

1. FDA Approved Label. Accessed January 22, 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020725s000lbl.pdf.

2. Othman MO, Harb D, Barkin JA. Introduction and practical approach to exocrine pancreatic insufficiency for the practicing clinician. *Int J Clin Pract*. 2018;72(2).

Pancreatic Enzyme Replacement Therapy (PERT) Is the Standard of Care for EPI



Administration

How is PERT administered?

PERT is orally administered as capsules or tablets and is taken during meals or snacks, with sufficient fluid.^{1,2} PERT should be swallowed whole and should not be crushed or chewed.

1. FDA Approved Label. Accessed February 21, 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022542s000lbl.pdf.
2. FDA Approved Label. Accessed February 21, 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020725s000lbl.pdf.

Pancreatic Enzyme Replacement Therapy (PERT) Is the Standard of Care for EPI



Mechanism of Action

What is the mechanism of action of PERTs?

The pancreatic enzymes in PERTs catalyze the hydrolysis of fats to glycerol and free fatty acids, proteins into peptides and amino acids, and starches into dextrans and short chain sugars in the duodenum and proximal small intestine, thereby acting like digestive enzymes physiologically secreted by the pancreas.

1. FDA Approved Label. Accessed January 22, 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020725s000lbl.pdf.

Pancreatic Enzyme Replacement Therapy (PERT) Is the Standard of Care for EPI



Dosage

What is the recommended dosage of PERT for patients with EPI?

PERT may be dosed based on fat ingestion or actual body weight. The initial starting dose and increases in the dose should be individualized based on clinical symptoms, the degree of steatorrhea present, and the fat content of the diet.

In children > 4 years and in adults, enzyme dosing should begin with 500 lipase units/kg of body weight per meal to a maximum of 2,500 lipase units/kg of body weight per meal (or < 10,000 lipase units/kg of body weight per day), or less than 4,000 lipase units/g fat ingested per day.

Usually, half of the prescribed dose for an individualized full meal should be given with each snack.

1. FDA Approved Label. Accessed January 22, 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020725s000lbl.pdf.

Treatment Insights

Physiology and
Prevalence

Causes of EPI

Symptoms
and Diagnosis

Burden

Treatment

Treatment
Insights

EPI Uncovered¹

Don't Let Digestive Discomfort Become the “New Normal”

- A survey conducted online by Harris Poll on behalf of the American Gastroenterological Association (AGA) and sponsored by AbbVie shed light on what the public and physicians know about the role of the pancreas in gastrointestinal (GI) health, and **exocrine pancreatic insufficiency (EPI)**.
- The EPI Uncovered survey was conducted with 1,001 adults who have experienced at least two GI issues three or more times in the past three months (patients) and 500 health-care practitioners, including 250 primary care physicians (PCPs) and 250 gastroenterologists (GIs).

60 to 70 million
people in the U.S.

live with digestive conditions,¹
and many are chronic.



Patients wait nearly
4 years

to see a doctor about
their GI symptoms,
on average.



WHY do they wait?

**3 out of
5 patients**

who found it difficult
to discuss their GI
symptoms with their
HCP (60%) said it was
due to embarrassment.

The survey suggests that speaking transparently
with a physician—and elevating the issue to a
gastroenterologist—may help to achieve the
right diagnosis the first time.



**But EPI is often not on
the radar**, even among those
with digestive discomfort...

2/3 of patients (66%) have
never heard of EPI.

78% are **not aware**
of what the
symptoms
of EPI are.

About 1 in 4
patients eventually
diagnosed with EPI
were **diagnosed with
a different condition
prior**, according to PCPs
(25%) and GIs (24%).

Patients' Insights²

PERT Dosing, Administration, and Follow-up

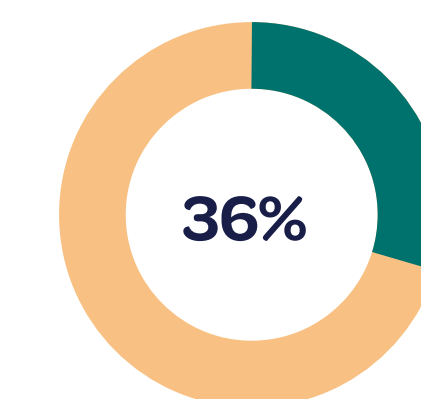
Data collected from patients with exocrine pancreatic insufficiency (EPI) indicate gaps in patients' understanding of dosage and administration of pancreatic enzyme replacement therapy (PERT), PERT dosing and patients' follow-up.

An IRB-approved online survey was conducted with 75 patients with EPI (or their caregivers).²

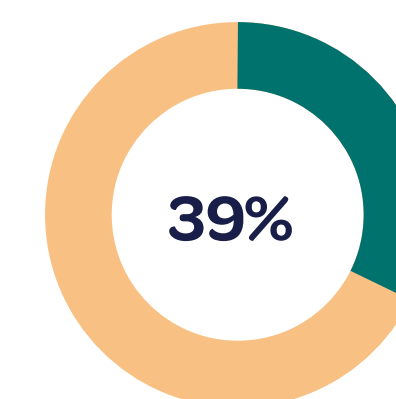
Patients' Assessment of EPI and PERT Understanding



Patients' Reports on PERT Dosing and Follow-up



Respondents taking PERT **doses lower than the dosing recommendations of the American College of Gastroenterology (ACG) Guidelines** for chronic pancreatitis (< 40,000 LU/meal)



Respondents reporting **absence of follow-up by their physician** since start of PERT

EPI=exocrine pancreatic insufficiency. HCP=healthcare professional. PERT=pancreatic enzyme replacement therapy. IRB=institutional review board.
1. EPI Uncovered. American Gastroenterological Association website. Published October 24, 2016. Accessed May 5, 2022. https://s3.amazonaws.com/agaemailassets/images/EPI_Uncovered_AGA_Survey_Infographic.pdf 2. Barkin JA, et al. *Am J of Gastroenterol*. 2021;116:S19-S20 3. National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Digestive Diseases Statistics for the United States. Accessed August 2016. <http://www.niddk.nih.gov/health-information/health-statistics/Pages/digestive-diseases-statistics-for-the-united-states.aspx>

