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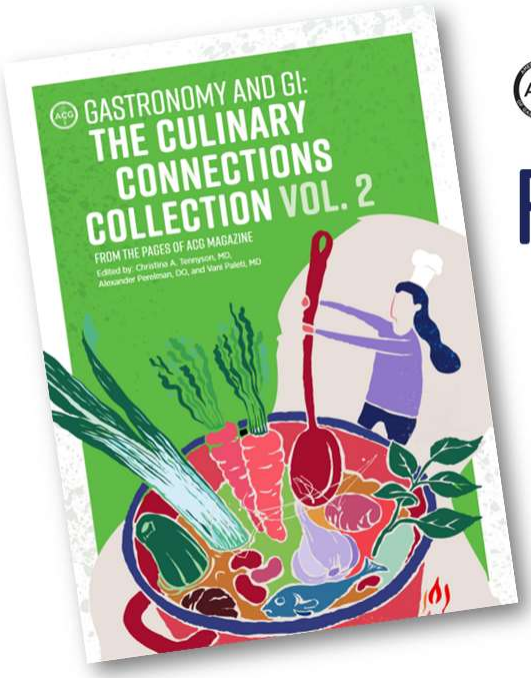

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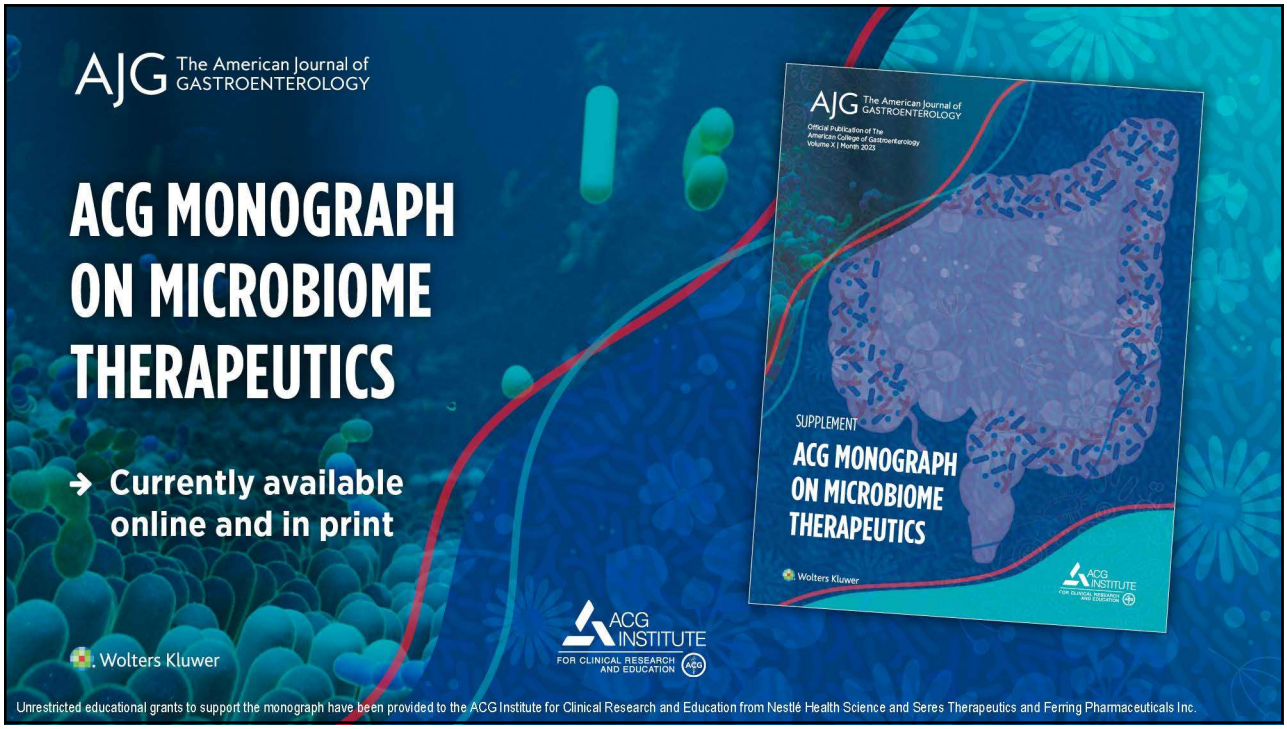
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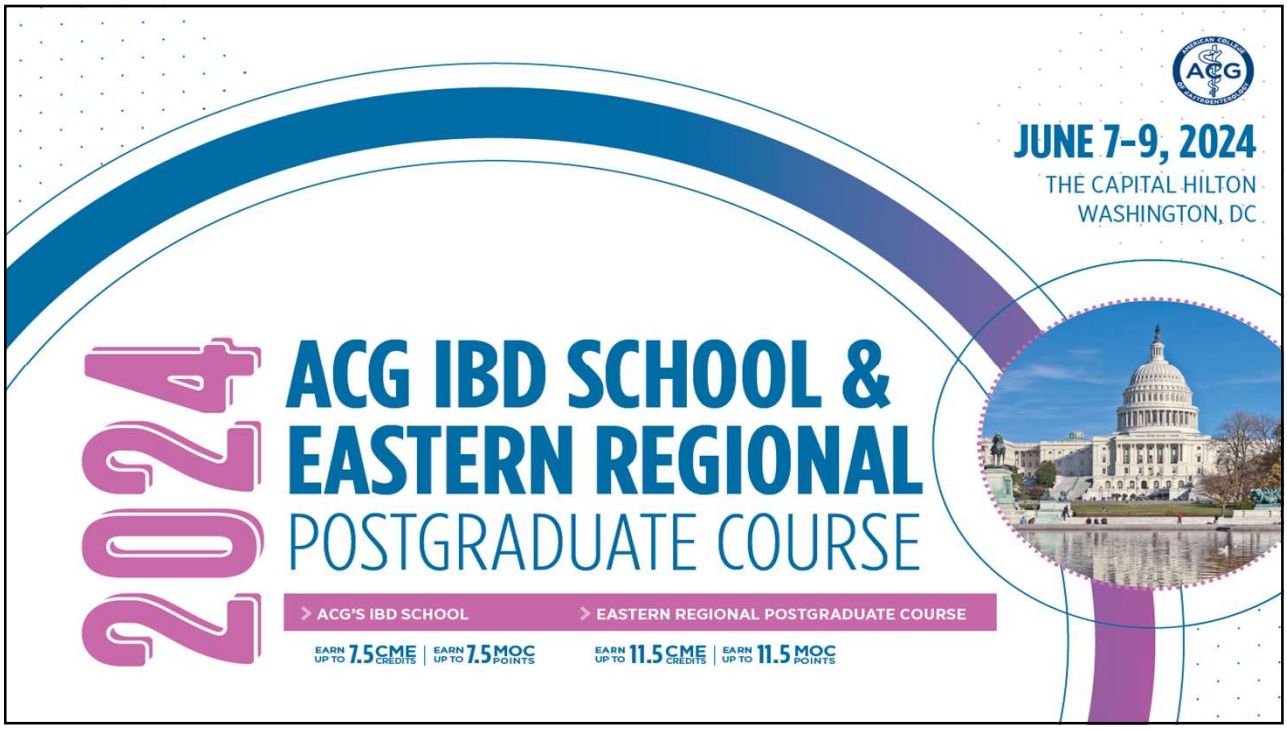
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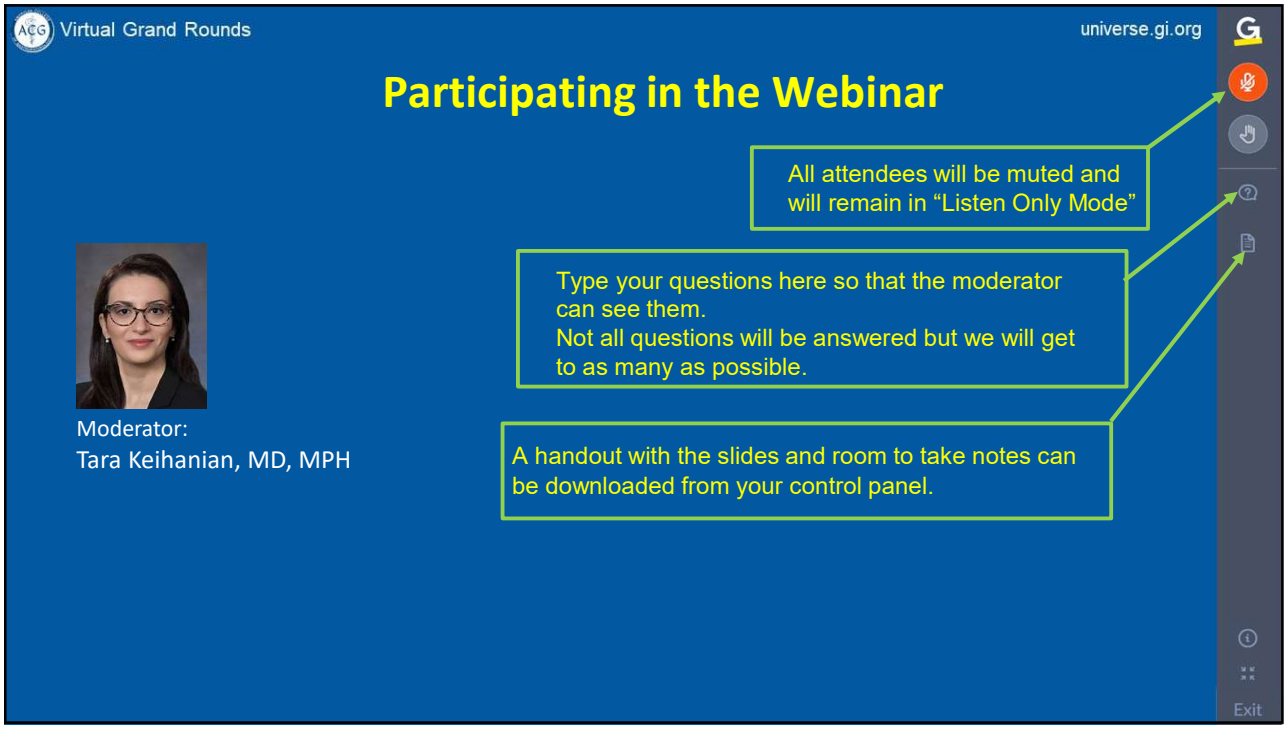
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All attendees will be muted and will remain in "Listen Only Mode"
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Not all questions will be answered but we will get to as many as possible.
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Moderator:
Tara Keihanian, MD, MPH
Exit

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Week 10 – Thursday, March 7, 2024
Application of Molecular and Genetic Testing to the Management of Colon Polyps and Cancer
Faculty: Aasma Shaukat, MD, MPH, FACG
Moderator: Pallavi Patil, MD
At Noon and 8pm Eastern


Week 9 – Thursday, March 14, 2024
Exocrine and Endocrine Complications of Pancreatitis
Faculty: Philip S. Schoenfeld, MD, MSEd, MScEpi, FACG
Moderator: Philip N. Okafor, MD, MPH, FACG
At Noon and 8pm Eastern

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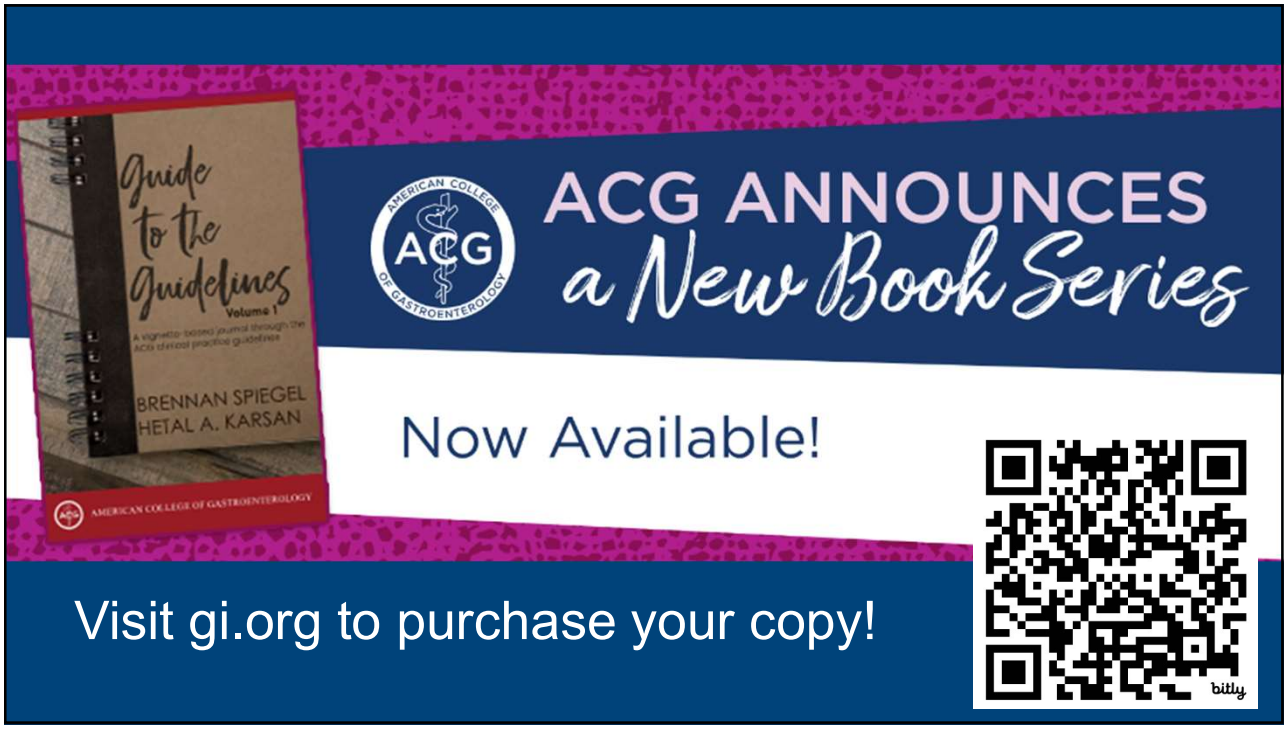

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Disclosures

Jodie A. Barkin, MD, FACG: Consultant: AbbVie, Aimmune/Nestle Health Sciences, CorEvitas LLC, Medtronic, Motus GI, Organon LLC, Exact Sciences; Research Grant: Cystic Fibrosis Foundation

Tara Keihanian, MD, MPH: Consultant for ConMed, Lumendi, Neptune Medical, and Boston Scientific.

**All of the relevant financial relationships listed for these individuals have been mitigated*

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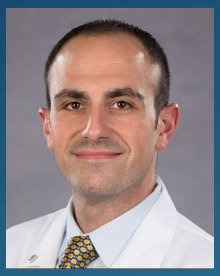
Exocrine and Endocrine Complications of Pancreatitis: Clinical Concepts to Advance Patient Care



Jodie A. Barkin, MD, FACG

Associate Professor of Clinical Medicine
Director of Pancreatic and Small Bowel Diseases
Medical Director, University of Miami Pancreas Center

University of Miami, Leonard M. Miller School of Medicine,
Department of Medicine, Division of Digestive Health and Liver Diseases,
Miami, Florida, USA

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Learning Objectives

- Identify the etiologies and recognize the symptoms of exocrine pancreatic insufficiency
- Explore the treatment of exocrine pancreatic insufficiency
- Describe endocrine pancreatic insufficiency (diabetes) in chronic pancreatitis
- Understand the impact and consequences of untreated exocrine pancreatic insufficiency and diabetes in pancreatic diseases

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Case Presentation

- 57y/oM, hx of recurrent acute pancreatitis x 4 (last episode 7 years prior) due to alcohol consumption with alcohol cessation 7 years ago
- Complains of chronic dull epigastric pain, worse post-prandially
- Associated bloating
- Notes a 15 pound unintentional weight loss in 6 months
- Bowel habits: 2 soft stools daily that float in the toilet bowl with small oil droplets floating in the water

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Case Presentation

Physical Exam:

- Vitals: T 36.8C; HR 84 bpm; RR 12; BP 108/74; O2 Sat 99% on room air, BMI 20.8
- Gen: AAOx3, NAD
- HEENT: NC/AT, Oral Mucosa Moist, Anicteric Sclera
- Neck: Supple, Trachea Midline, no JVD
- Cardio: regular rate and rhythm, no M/R/G
- Pulm: Breathing comfortably; CTAB
- Abdomen: Bowel sounds present, soft, nondistended, minimal epigastric tenderness, no rebound, no guarding, no hepatosplenomegaly, no Murphy's sign
- Ext: 2+ pulses bilaterally, no peripheral edema
- Neuro: AAOx3, non-focal.
- Psych: Normal mood and affect, no SI/HI

Labs:

- CBC: normal
- CMP: normal; normal Cr and LFTs
- Lipase: 48 U/L
- CA 19-9: 5 U/mL (normal <37)
- INR 1.4
- Vitamin D (25-OH): 20 ng/mL (normal >30)
- Vitamin A & E normal
- Hemoglobin A1C: 7.1%
- Fecal Elastase: 23 µg/g (Normal: >200 µg elastase/g fecal material; moderate pancreatic insufficiency 100-200µg/g; severe pancreatic insufficiency <100 µg/g)

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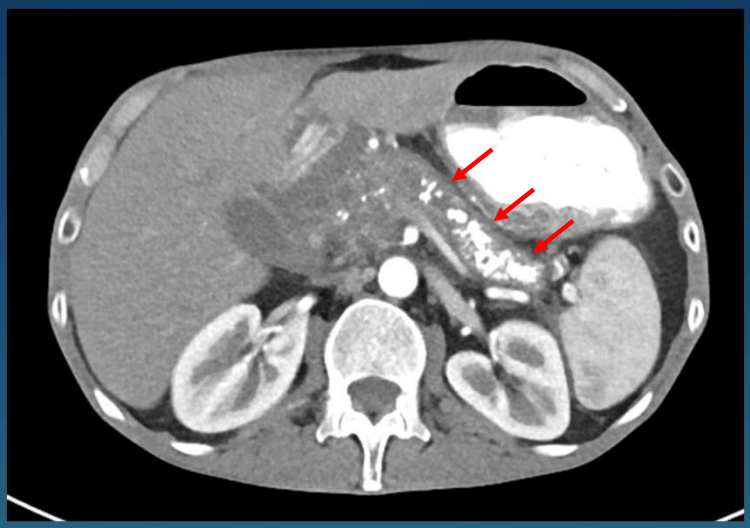

A diagnosis of chronic pancreatitis with exocrine pancreatic insufficiency is made

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Exocrine Pancreatic Insufficiency: Definition

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- Exocrine Pancreatic Insufficiency a.k.a. ***EPI***

New Proposed Definition of EPI (AGA-PancreasFest 2021)*:

- *Essence*: Failure of pancreas to deliver minimum level of pancreatic digestive enzymes to the intestine to meet the nutritional/metabolic needs of that patient
  - Impacted by macro/micro-nutrient needs, nutrient intake, exocrine pancreas function, and intestinal anatomy/function/absorptive capacity
- *Character*:
  - Variable deficiencies in micro- and macro-nutrients (essential fats & fat-soluble vitamins)
  - GI symptoms of maldigestion
  - Improvement with Pancreatic enzyme replacement therapy (PERT), diet/lifestyle changes, and disease treatment
- Normal pancreatic function will produce approximately 700,000 lipase units per meal (varies by meal)
- Fat maldigestion when < 10% of residual lipase function

Whitcomb DC, et al. AGA-PancreasFest Joint Symposium 2021.
Lindkvist B. *World J Gastroenterol*. 2013;19:7258-7266.
Sikkens E, et al. *Best Pract Res Clin Gastroenterol*. 2010;24(3):337-347.
Lohr JM, et al. *UEG Journal*. 2017;5(2):153-199.
Keller J, Layer P. *Gut*. 2005;54(suppl 6):1-28.
Domínguez-Muñoz JE. *Adv Med Sci*. 2011;56(1):1-5.
DiMagno EP. *NEJM*. 1973;288:813-815.
DiMagno EP, Go VL. *Postgrad Med*. 1972;52(1):135–40.

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Exocrine Pancreas Physiology: Part 1

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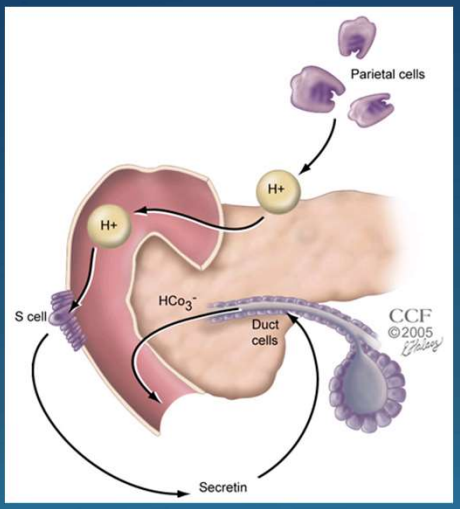

Phase	Mediator	Secretion %
Cephalic	Vagus	20-25%
Gastric	Food in stomach & Vagus	10%
Intestinal	Hormonal (secretin & CCK) & neural	50-80%
Absorbed nutrient	Amino acids may promote secretion	

Chandra R, Liddle RA. Regulation of Pancreatic Secretion. *Pancreapedia* **2015.**
Figure: UpToDate, Courtesy of Dr. Tyler Stevens & the Cleveland Clinic Foundation

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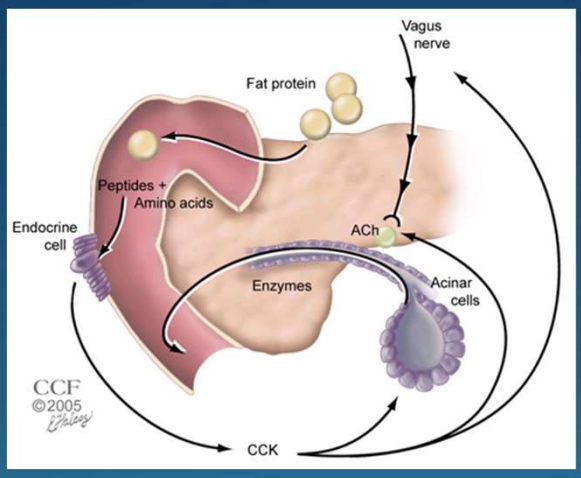
Exocrine Pancreas Physiology: Part 2



- Normal pancreatic function will produce approximately 700,000 lipase units per meal (varies by meal)
- Fat maldigestion when < 10% of residual lipase function

Keller J, Layer P. *Gut*. 2005;54(suppl 6):1-28.
Domínguez-Muñoz JE. *Adv Med Sci*. 2011;56(1):1-5.
DiMagno EP. *NEJM*. 1973;288:813-815.
DiMagno EP, Go VL. *Postgrad Med*. 1972;52(1):135–40.
Figure: UpToDate, Courtesy of Dr. Tyler Stevens & the Cleveland Clinic Foundation

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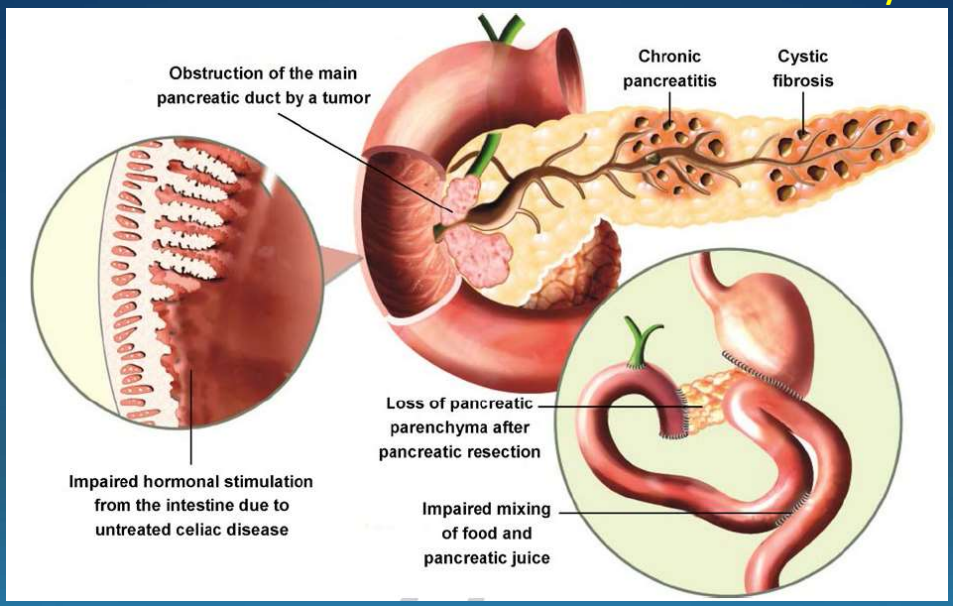
Causes of Exocrine Pancreatic Insufficiency



Lindkvist B. *World J Gastroenterol* 2013;19(42):7258-66

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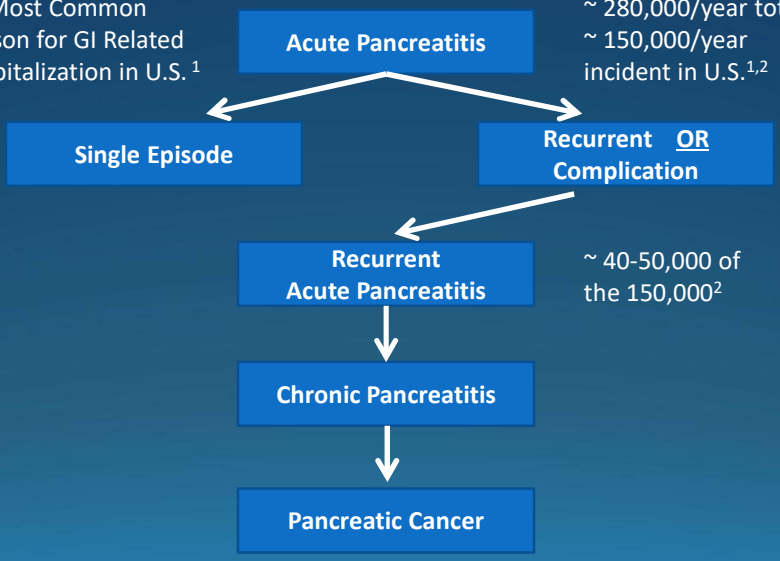
Overall Progression of Pancreatic Disease

3rd Most Common Reason for GI Related Hospitalization in U.S. [1]



~ 280,000/year total; ~ 150,000/year incident in U.S.[1,2]

~ 40-50,000 of the 150,000[2]

1. Peery AF, et al. Gastroenterology 2019;156(1):254-72.e11
2. Cote GA, et al. Am J Gastroenterol 2018;113:906-912.

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Development of EPI After Acute Pancreatitis

- Study Design: Systematic Review & Study Level Meta-Analysis of 32 Studies of 1495 AP Pts evaluating development of EPI after AP[1]

Results:

- **Pooled EPI Prevalence After AP: 27.1%** (95% CI 20.3-35.1%)
- EPI more common in **Alcoholic AP** than Biliary AP or other AP etiologies using Fecal Elastase testing (22.7% vs. 10.2% vs. 13.4%; **p=0.02**)
- EPI more common after **severe AP** than mild AP (33.4% vs. 19.4%; **p=0.049**)
- EPI somewhat more common if **necrosis** present (32.0% vs. 18.9%; **p=0.053**)
- Findings confirmed in a subsequent systematic review and meta-analysis of 39 studies of 1795 pts, EPI prevalence of approximately 35% after AP; and more prevalent in Alcoholic etiology, severe AP and with necrosis present[2].

1. Hollemans RA, et al. Pancreatology 2018;18(3):253-262.
2. Huang W, et al. Dig Dis Sci 2019;64(7):1985-2005.

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Exocrine Pancreatic Insufficiency (EPI) in Chronic Pancreatitis

- Etiology:
  - Destruction of pancreatic parenchyma and loss of acinar cells
  - Obstruction of the pancreatic duct secondary to strictures and stones
- Prevalence and severity of EPI increases with duration of CP
  - 6-22% at time of CP diagnosis
  - 28% by 5 years post-CP diagnosis
  - 50% by 12 years post-CP diagnosis
- More common in alcoholic than non-alcoholic CP (41% vs. 19%)

Duggan S, et al. *Nutr Clin Prac*. 2010;25:362-370.
Muniraj T, et al. *Dis Month*. 2014;60:530-550.
Lindkvist B. *World J Gastroenterol*. 2013;19:7258-7266.
Layer P, et al. *Gastroenterology*. 1994;107(5):1481-1487.
Machicado JD, et al. *Pancreatology*. 2018;18(1):39-45.
Sandhu BS, et al. *Clin Gastroenterol Hepatol*. 2007;5(9):1085-1091.

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Exocrine Pancreatic Insufficiency in Pancreatic Cancer

Resectable Pancreatic Cancer:

- 25-45% have pre-operative EPI
- 50-80% of patients continue to experience EPI after pancreatic surgery

Unresectable PC:

- EPI is common (>50%) and progressive over time

Sikkens ECM, et al. *Br J Surg*. 2014;101(2):109-113.
Matsumoto J, et al. *J Gastrointest Surg*. 2006;10(9):1225-1229.
Park JW, et al. *Br J Surg*. 2013:100(8):1064-1070.
Sikkens EC, et al. *J Clin Gastroenterol*. 2014;48:e43-e46.
Bartel MJ. *Dig Liver Dis*. 2015;47(12):1013-1020.
Tseng DS, et al. *Pancreas*. 2016;45(3):325-30.

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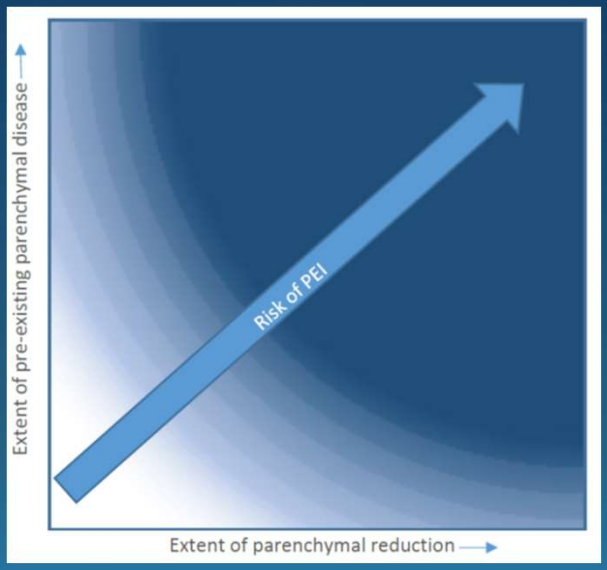
Development of EPI Post-Pancreatic Surgery



Australasian Pancreatic Club Pancreatic Enzyme Replacement Therapy Guidelines 2015. Working Party of the Australasian Pancreatic Club, et al. *Pancreatology*. 2016;16(2):164-80.

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EPI in Celiac Disease

- Prevalence of Celiac Disease in U.S.: ~ 1%
- Pathophysiology: Celiac Disease → small bowel mucosal damage → impaired enteric mediated hormonal stimulation to pancreas (CCK) and loss of enterokinase → EPI
- Aim: Determine prevalence of EPI in Celiac Disease at diagnosis & with gluten free diet treatment
- Methods: Systematic review & Meta-analysis
- Population: 460 Celiac disease pts; 34% male, mean age 44.1 years

Jiang C, Barkin JA, Barkin JS. Dig Dis Sci 2023;68(8):3421-7.

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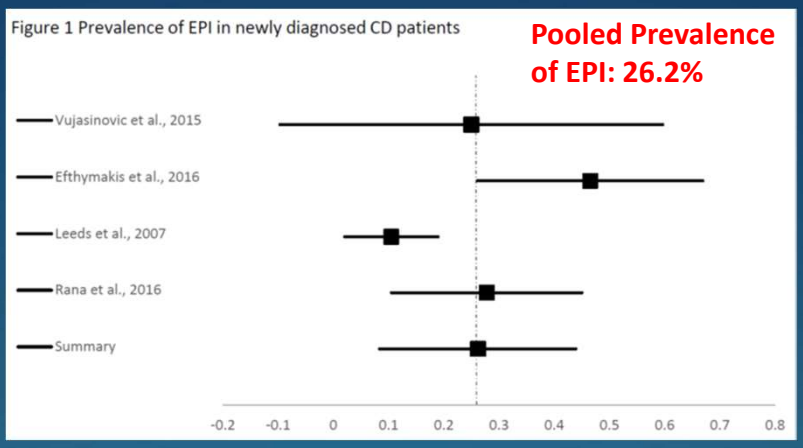
EPI in Newly Diagnosed Celiac Disease



- Prevalence Range: 10.5% - 46.5%
- Pooled: 26.2% (95% CI 8.43%-43.92%, Q = 2.24, I^2 = -33%)

Jiang C, Barkin JA, Barkin JS. Dig Dis Sci 2023;68(8):3421-7.

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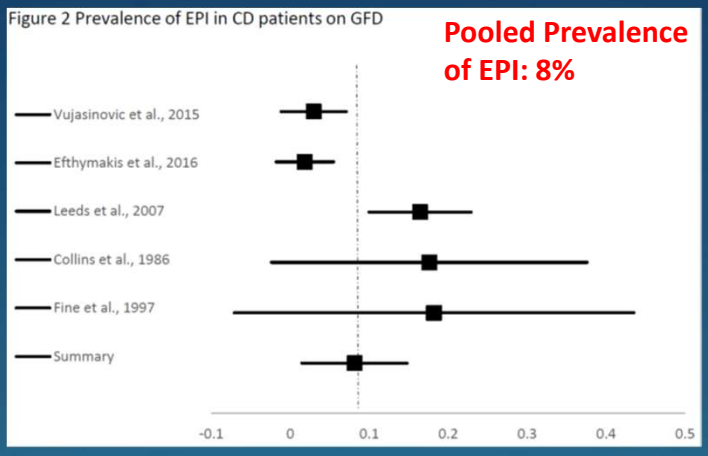
EPI in Celiac Disease Patients on Gluten-Free Diet



- Prevalence Range: 1.9% to 18.2%
- Pooled: 8% (95% CI 1.52% - 14.8%, Q = 4.42, I^2 = 9.59%)

Jiang C, Barkin JA, Barkin JS. Dig Dis Sci 2023;68(8):3421-7.

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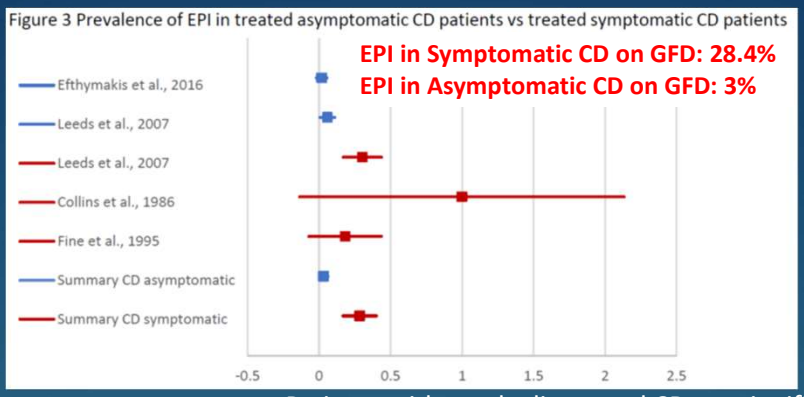
Symptomatic Celiac Disease Increases EPI Prevalence



- Patients with newly diagnosed CD are significantly more likely to have EPI compared to those patients treated with GFD (p = 0.031).
- Prevalence of EPI: Symptomatic CD patients on GFD (28.4%) vs. Asymptomatic CD patients on GFD (3%) (P<0.001)

Jiang C, Barkin JA, Barkin JS. Dig Dis Sci 2023;68(8):3421-7.

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SIBO Prevalence in Chronic Pancreatitis with EPI

- Aim: Determine the prevalence of SIBO in pts with chronic pancreatitis and mild to severe EPI
- Methods: 35 pts with CP and EPI and 31 matched controls underwent breath hydrogen testing for SIBO

Results:

- SIBO Prevalence in CP with EPI: 15% (vs. 0% in controls; p=0.029)
- Factors significantly increasing likelihood of SIBO in CP:
  - PERT use (p 0.029)
  - PPI use (p 0.022)
  - Alcoholic etiology of CP (p 0.023)
  - Concurrent diabetes (p 0.009)
- No significant differences in symptoms in SIBO + vs -

Chonchubhair HMN, et al. Pancreatology 2018;18(4):379-385.

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SIBO Prevalence in CP and Effect of EPI: Meta-Data

- Aim: Establish prevalence of & factors influencing development of SIBO in CP
- Methods: Systematic review & meta-regression with random effects model
- Study Population: 13 studies of 518 patients with CP undergoing SIBO testing

Results:

- SIBO Pooled Prevalence in CP: 38.6% (EPI & type of diagnostic test for SIBO accounted for variance)
- Increased risk of SIBO in CP vs. controls (OR 5.58)
- Increased risk of SIBO in CP if Diabetic (OR 2.1) or EPI present (OR 2.5)
- 76% had improvement of symptoms after SIBO treatment (primarily with Rifaximin)

El Kurdi B, et al. Clin Translational Gastroenterol 2019;10:e00072

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EPI Prevalence Varies by Etiology

Condition	Estimated prevalence
Chronic pancreatitis[9]	30% in patients with mild disease; 85% with severe disease
Cystic fibrosis[19]	Approximately 85% of newborns
Diabetes[68]	
Type 1	26%-44%
Type 2	12%-20%
HIV/AIDS[14,69]	26%-45%
Intestinal disorders[14,23]	
Irritable bowel syndrome	4%-6%
Coeliac disease	12%-30%
Inflammatory bowel disease	19%-30%
Inoperable pancreatic cancer[20]	50%-100%
Surgery[21]	
Distal pancreatectomy	19%-80%
Whipple surgery	56%-98%
Shwachman-Diamond syndrome[28]	82%
Johanson-Blizzard syndrome[29]	High

Othman MO, Harb D, Barkin JA. *Int J Clin Pract* 2018;72(2):e13066.

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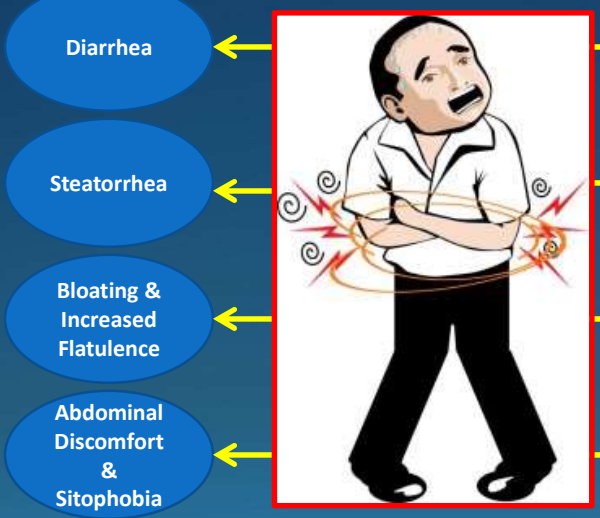
Clinical Symptoms of Exocrine Pancreatic Insufficiency



Pezzilli R, et al. *World J Gastroenterol.* 2013;19:7930-7946.
Keller J, Layer P. *Gut*. 2005;54(Suppl VI):vi1-vi28.

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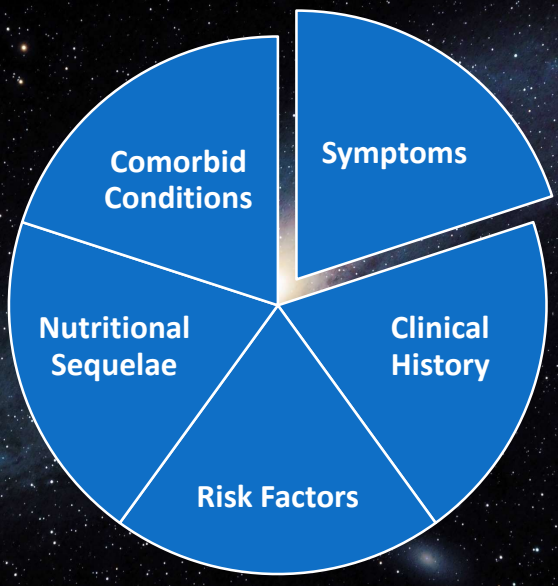
EPI: Diagnosis Using a Constellation of Factors



Othman MO, Harb D, Barkin JA. *Int J Clin Pract* 2018;72(2):e13066.

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Diagnosis of Exocrine Pancreatic Insufficiency

- Quantitative 72-hour fecal fat (using a standardized fat intake diet)
- Endoscopic pancreatic function testing via Dreiling tube/endoscopy (+/- use of secretin) – measuring bicarbonate secretion
- Secretin enhanced MRCP pancreatic function testing
- **Fecal elastase-1 (FE-1) (Traditionally EPI < 200 mcg/g)**
  FE-1 performance characteristics by meta-analysis[1]:
  - FE-1 vs. Secretin Stimulation: FE-1 sensitivity 77%, specificity 88%
  - FE-1 vs. Quant Fecal Fat: FE-1 sensitivity 96%, specificity 88%
  - If low EPI probability (5%), FE-1 false neg = 1.1%, false pos = 11%
  - If high EPI probability (40%), FE-1 false neg = ~ 10%
- Fecal chymotrypsin (less sensitive than FE-1)
- Breath testing via 13-C mixed triglyceride marked substrates (unavailable in US)
- Imaging severity of CP does not correlate with presence or severity of EPI

Don't Forget… Perform FE-1 testing on solid stool to reduce false positive results

1. Vanga RR, et al. *Clin Gastroenterol Hepatol*. 2018;16:1220-8.
2. Lohr JM, et al. *UEG Journal*. 2017;5(2)153-99.

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Pancreatic Enzyme Replacement Therapy Corrects Nutritional Deficiencies in Chronic Pancreatitis

The Solution to EPI is…
Pancreatic Enzyme Replacement Therapy (PERT)

- **PERT to be taken WITH meals**
- Approximately **36,000-80,000 units of lipase per meal** (half for snacks)
- In a meta-analysis of 17 studies of 511 CP patients, PERT significantly improved coefficient of fat absorption compared to baseline ($p<0.00001$) and placebo ($p=0.0001$), and reduced fecal fat excretion
- No significant adverse events with PERT
- PERT improves nutritional parameters, GI symptoms, and quality of life
- High-dose or enteric-coated enzymes more effective than low-dose or non-coated

De La Iglesia-Garcia D, et al. Gut 2017;66(8):1354-1355

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Types of Pancreatic Enzyme Replacement Therapy

Enteric Coated Capsule
- Creon®
- Zenpep®
- Pancreaze®
- Ultresa®
- Pertzye®

Cartridge-Based Device
- Relizorb®

Non-Enteric Coated Tablet (Need PPI Co-Administration)
- Viokace™

- Initial FDA regulations of PERT: 1991
- Actual initiation of FDA regulations/approval: 2004-2010
- Risk: Fibrosing colonopathy
  - If > 2,500 lipase units/kg/meal
  - If > 10,000 lipase units/kg/day

https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/updated-questions-and-answers-healthcare-professionals-and-public-use-approved-pancreatic-enzyme. Accessed March 31, 2021.

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CLINICAL GUIDELINES

PMID 32022720

ACG Clinical Guideline: Chronic Pancreatitis **2020**

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Am J Gastroenterol 2020;115:322-339. https://doi.org/10.14309/ajg.0000000000000535; published online February 5, 2020

1. We suggest PERT in patients with CP and exocrine pancreatic insufficiency to improve the complications of malnutrition.
2. Patients with CP should have periodic evaluation for malnutrition including tests for osteoporosis and fat-soluble vitamin deficiency.
3. We do not suggest the use of pancreatic enzyme supplements to improve pain in CP.
4. PERT should include an adequate dosage (at least 40,000–50,000 USP units of lipase with each meal) administered during the meal.

Gardner TB, et al. *Am J Gastroenterol*. 2020;115:322-339.

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PERT Initial Dosing & Adjustment

Society Sponsoring Guideline	Year	PERT Starting Dose
American College of Gastroenterology [1]	2020	40,000-50,000 units TID with meals (half dose with snacks)
United European Gastroenterology [2]	2017	40,000-50,000 units TID with meals (half dose with snacks)
Australasian Pancreatic Club [3]	2015	25,000-40,000 units TID with meals (10,000 units with snacks)
Japanese Society of Gastroenterology [4]	2015	Initial dosing not mentioned

- PERT should be administered with meal (not before or after)
- PERT "non-responders" management:
  - Ensure PERT compliance/correct administration
  - Consider increasing dose
  - Consider adding PPI
  - Consider switching PERT type/formulation
  - Ensure no other comorbid conditions, i.e. SIBO

1. Gardner TB, et al. *Am J Gastroenterol*. 2020;115:322-339.
2. Lohr JM, et al. *UEG Journal*. 2017;5(2)153-99.
3. Working Party of the Australasian Pancreatic Club, et al. *Pancreatology*. 2016;16(2):164-80.
4. Ito M, et al. *J Gastroenterol*. 2016;51:85-92.

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PERT Treats EPI-Associated Symptoms and Malabsorption in Chronic Pancreatitis

- Aim: Evaluate improvement in EPI in patients with CP taking PERT for coefficient of fat absorption (CFA) and clinical symptoms (stool frequency, consistency, abdominal pain & flatulence)
- Methods: Post-hoc analysis of 2 double-blind, randomized, placebo-controlled trials of PERT (pancrelipase) x1 week + 51-week OLE in subjects with CP followed by ANOVA analysis for symptoms response calculations.
- Study Population:
- 116 CP patients (59 treated with PERT & 57 with placebo)
- 86 (74%) men, median age 47 years

Barkin JA, et al. *Pancreas*. 2021;50(2):176-82.

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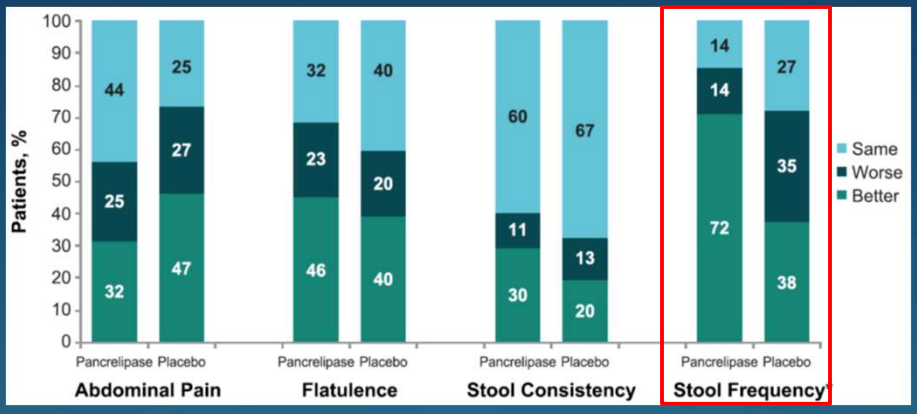
PERT Treats EPI-Associated Symptoms and Malabsorption in Chronic Pancreatitis



- Treatment with PERT vs. Placebo significantly improved stool frequency at week 1 (71.9% vs. 38.2%; p=0.001)

Barkin JA, et al. *Pancreas*. 2021;50(2):176-82.

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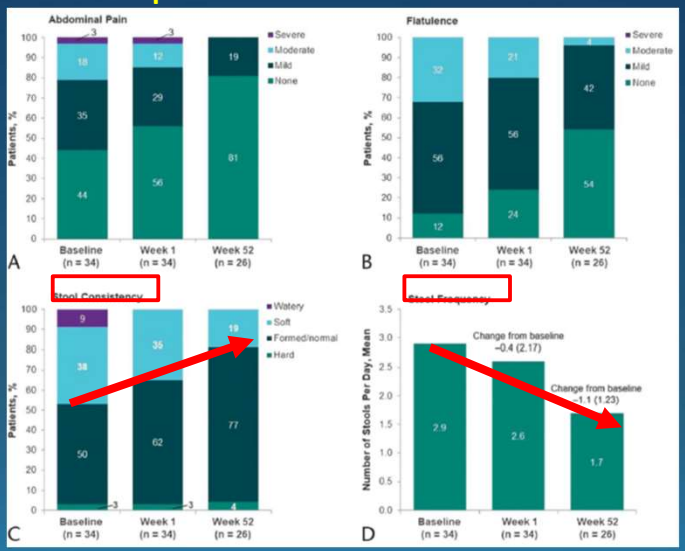
PERT Treats EPI-Associated Symptoms and Malabsorption in Chronic Pancreatitis

Stool consistency and frequency significantly improved with PERT, with durable 52-week response



Barkin JA, et al. *Pancreas*. 2021;50(2):176-82.

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PERT Treats EPI-Associated Symptoms and Malabsorption in Chronic Pancreatitis

TABLE 2. *P* Values From ANOVA for Between-Group Comparison of Change From Baseline in CFA or MSF and Symptom Response

	Change in CFA		Change in MSF	
	Symptom Improved vs Not Improved*	Pancrelipase vs Placebo†	Symptom Improved vs Not Improved*	Pancrelipase vs Placebo†
Symptom	*P*	*P*	*P*	*P*
Abdominal pain	0.842	<0.001	0.850	<0.001
Flatulence	0.282	<0.001	0.058	<0.001
Stool consistency	0.030	<0.001	0.033	<0.001
Stool frequency	<0.001	<0.001	<0.001	<0.001

- **Stool Coefficient of Fat Absorption and Mean Stool Fat improved with PERT**
- On ANOVA, improvement in stool frequency and consistency positively correlated with improvement in CFA and mean stool fat.
- PERT use did not affect significant changes in abdominal pain & flatulence.
- **Improved stool frequency and consistency may serve as surrogate clinical markers of response to PERT.**

Barkin JA, et al. *Pancreas*. 2021;50(2):176-82.

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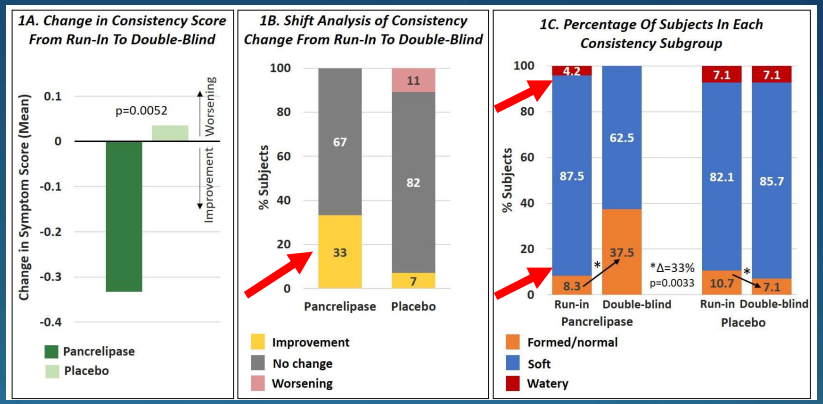
PERT Improves EPI-Associated Patient-Reported Symptoms in Chronic Pancreatitis or Pancreatic Surgery

52 pts with CP or pancreatic surgery (PS) in a Double-Blind Randomized Trial of PERT vs placebo for EPI symptoms

Change in Stool Frequency

	Pancrelipase (n=24)	Placebo (n=27)
Number of stools/day, mean (SD)		
Run-in placebo period	3.7 (2.41)	3.5 (1.40)
Double-blind treatment period	2.1 (0.85)	3.1 (1.33)
Change in number of stools/day, mean (SD)		
From run-in to double-blind period	–1.6 (2.39)	–0.4 (1.05)
Treatment difference (95% CI)	–1.206 (–2.284, –0.128) p=0.0296	

Change in Stool Consistency



Conclusions: PERT → Decreased # of stools, Improved consistency of stools, Eliminates watery stools

Barkin JA, et al. ACG 2022 Abstract C0005.

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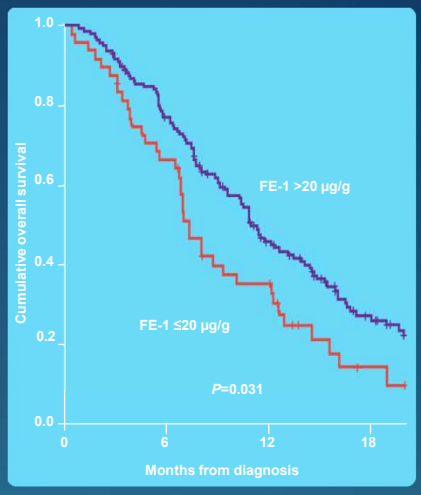
Consequences of Exocrine Pancreatic Insufficiency

- Nutritional Consequences[1]
  - Deficiencies in fat-soluble vitamins (A, D, E, K) and Vitamin B-12
  - Bone Disease
  - Weight loss
  - Malnutrition
- Impaired quality of life[2]
- Increased mortality in advanced pancreatic cancer[3]
  - If fecal elastase-1 ≤20 µg/g, Median survival 7 vs. 11 months, p=0.031
- Substantial weight loss (>10%) worsens pancreatic cancer survival[4]



1. Pezzilli R, et al. *World J Gastroenterol.* 2013;19:7930-7946.
2. Keller J, Layer P. *Gut*. 2005;54(Suppl VI):vi1-vi28.
3. Partelli S, et al. *Dig Liver Dis*. 2012;44:945-951.
4. Nemer L, et al. Pancreas 2017;46(9):1152-1157.

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EPI in Chronic Pancreatitis Is Associated with Increased Risk of Cardiovascular Events

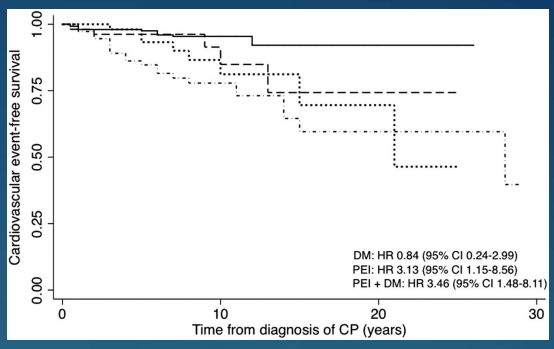
- Aim: To evaluate the risk of cardiovascular (CV) events in a CP cohort and evaluate the association with EPI.
- Methods: Prospective, longitudinal cohort study of 433 CP patients in Spain (Mean age 47.8 ± 14.4 years of age; 79.1% male; Mean follow-up was 8.6 ± 4.6 years).

Conclusions:

- Higher incidence of CV events if EPI present
  - Incidence Rate Ratio 3.67, 95% CI 1.92-7.24, p<0.001

Increased CV risk on Multivariate Analysis if:

- EPI without DM (OR 4.96; 95% CI 1.68-14.65)
- Coexistence of EPI and DM (OR 6.54; 95% CI 2.71-15.77)
- Hypertension (OR 3.40; 95% CI 1.50-7.72)
- Smoking (OR 2.91, 95% CI 1.07-7.97)



De La Iglesia D, et al. J Gastroenterol Hepatol. 2019;34(1):277-83.

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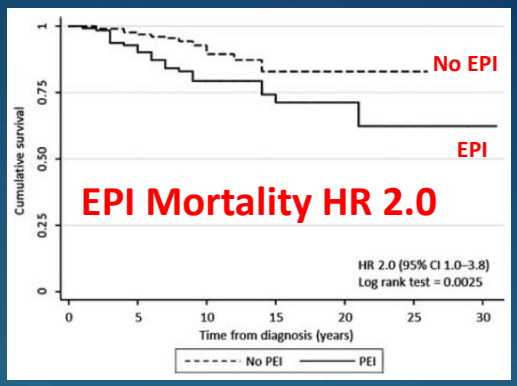
EPI in Chronic Pancreatitis Is Associated with Increased Risk of Mortality

- Aim: Assess mortality risk of EPI in CP patients
- Methods: prospective longitudinal cohort study of 430 CP patients (79.1% M; mean age 47.8 yrs; mean follow up 8.6±4.6 yrs)

Conclusions: EPI is associated with increased:

- Mortality (HR 2.59; p<0.003)
- Cirrhosis (HR 3.87; p<0.001)
- Age at diagnosis (HR 1.05; p<0.001)
- Toxic etiology of CP (HR 3.11; p<0.05)
- Respiratory comorbidities (HR 2.19; p<0.03)
- Lower nutritional markers in EPI vs. non-EPI (p<0.001) and in pts who died vs. survived (p<0.001)



De La Iglesia D, et al. J Clin Gastroenterol. 2018;52(8):e63-e72.

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Anthropomorphic Effects of EPI in CP

Weight:

- EPI is associated with being underweight[1]
- On multivariate analysis, presence of EPI was significantly and independently associated with lower BMI

Muscle Mass:

- EPI significantly increases risk for sarcopenia[2,3]
- Presence of sarcopenia also increases risk for EPI (76% of CP pts with sarcopenia had EPI; OR 3.8, 95%CI 1.2-12.5, p=0.003)

1. Olesen SS, et al. *Nutrition*. 2017;43-44:1-7.
2. Olesen SS, et al. *Pancreatology*. 2019;19(2):245-251.
3. Shintakuya R, et al. *Pancreatology*. 2017;17:70-75.

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Metabolic Bone Disease in CP Patients with EPI

- Decreased bone mineral density is common in CP and increased in those with EPI[1,2]
- Pooled Prevalence of Bone Disease in CP (Systematic Review & Meta-Analysis of 513 pts): Osteopenia 40%; Osteoporosis 23%[3]
- Osteoporosis is increased in CP compared to matched controls (34% vs. 10%)[4]
- Low-trauma fractures are common in CP (4.8% Prevalence) and significantly increased (HR 2.0, $p<0.0001$) compared to matched controls[5,6]
- Treatment with PERT in CP decreased fracture risk (HR 0.8)[6]
- Treatment with PERT is associated with significantly improved bone density via DEXA score ($p<0.05$)[7]

1. Barkin JA, et al. J Clin Densitom. 2020;23(2):237-43.
2. Sikkens ECM, et al. *Pancreatology.* 2013;13(3):238-242.
3. Duggan SN, et al. Clin Gastroenterol Hepatol 2014;12:219-228.
4. Duggan SN, et al. Pancreas 2012;41(7):1119-1124
5. Tignor AS, et al. Am J Gastroenterol 2010;105:2680-2686.
6. Bang UC, et al. Clin Gastroenterol Hepatol 2014;12:320-326.
7. Haas S, et al. JOP 2015;16(1):58-62

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The Economic Burden of Illness Associated with EPI

- 7,366 patients with EPI on pancreatic enzyme replacement therapy (PERT) matched with a cohort of 22,089 control patients without EPI[1]

Conclusions:

- Patients with EPI had significantly higher direct healthcare costs than non-EPI controls ($p<0.001$)
- There were no significant differences in costs due to workplace absence in EPI vs non-EPI controls
- Patients with EPI had significantly higher indirect costs due to short-term disability and long-term disability than non-EPI controls in 12-month follow up period ($p<0.001$)
- A separate pharmaceutical claims database study of 819 pancreatic cancer pts looking at early PERT initiation (< 3weeks) post-Whipple demonstrated significantly lower total healthcare costs in those receiving PERT vs. no PERT ($96,334 vs. $106,820; p= 0.0348)[2]

1. Durden E, et al. APA 2017 #P1-114. Pancreas 2017;46(10):1398.
2. Khandelwal N, et al. Am J Gastroenterol 2018;113:S53-S54.

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Healthcare Resource Utilization in EPI

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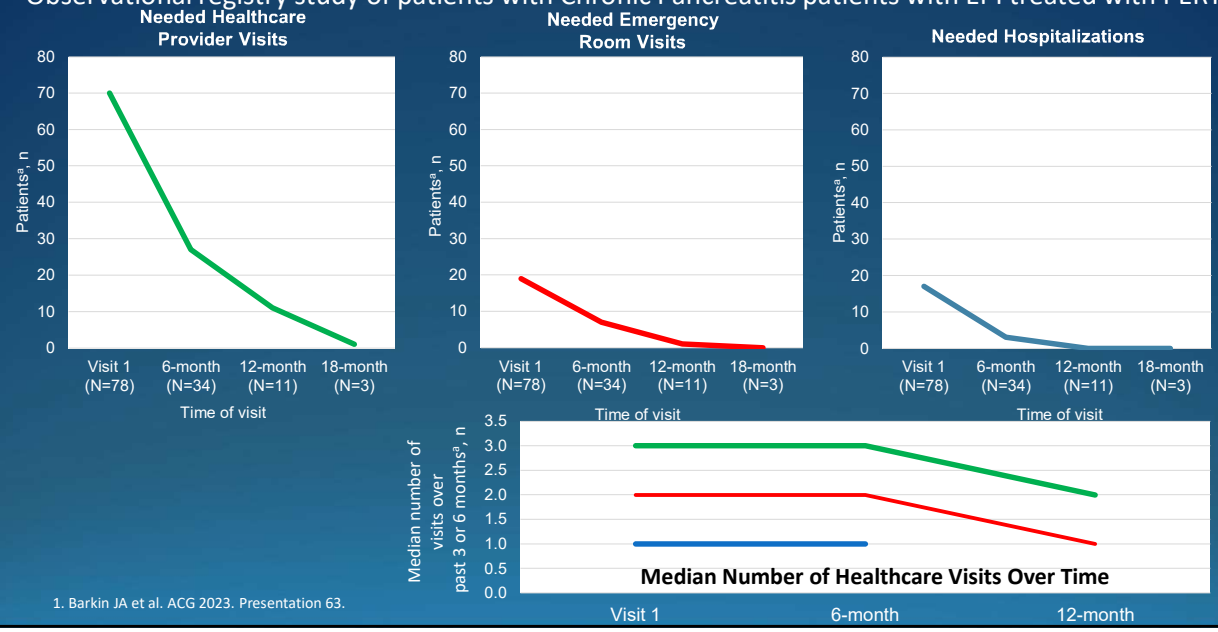
- Observational registry study of patients with Chronic Pancreatitis patients with EPI treated with PERT



1. Barkin JA et al. ACG 2023. Presentation 63.

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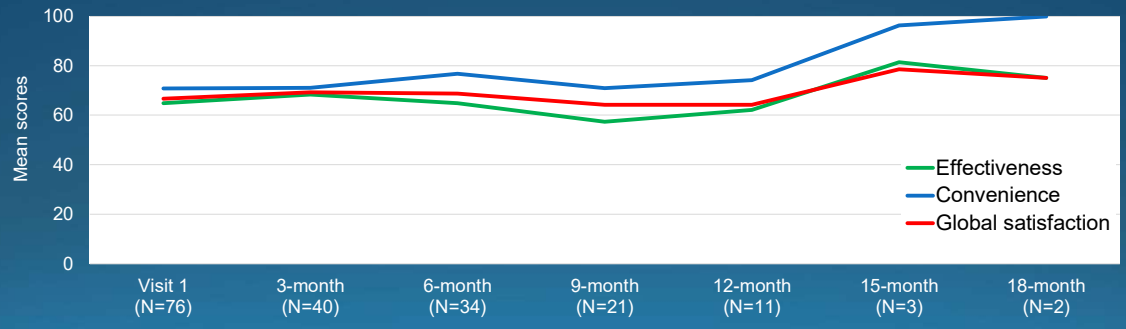
EPI Treatment Satisfaction and Workplace Absenteeism

- Observational registry study of patients with Chronic Pancreatitis patients with EPI treated with PERT
- Full-time employees took a median of 2.5 days off over the past 3 months at Visit 1 (n=28); days off at subsequent visits were ≤2.0
- Mean global treatment satisfaction scores fluctuated and generally improved from Visit 1 to subsequent visits

Treatment Satisfaction Over Time



1. Barkin JA, et al. ACG 2023. Presentation 63.

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Barriers to EPI Diagnosis

- Average of 3.7 years before pts sought care
- Median of 4 visits before making EPI diagnosis
- Lack of Awareness:
  - 2/3 of Patients haven't heard of EPI
  - 78% of patients don't know EPI-associated symptoms
  - **1 in 4 patients was diagnosed with a different condition before EPI diagnosis** (25% for PCP, 24% for GI)
- Communication & Knowledge Improve Care:
  - Gastroenterologists understand EPI (98% have diagnosed a patient with EPI)
  - 78% of PCPs and 92% of GIs surveyed believed EPI symptom patient education should be done by GI
  - 84% of PCPs and 93% of GIs surveyed believed all of most of EPI treatment should be done by GI

American Gastroenterological Association website. http://www.gastro.org/press_releases/largest-analysis-examining-barriers-to-epi-diagnosis-finds-patients-with-digestive-health-issues-overlook-their-symptoms. Accessed March 20, 2021.

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Appropriate Use of PERT in Pancreatic Cancer Patients Is Low, But Improves Symptoms & Weight Loss

PANCREATIC CANCER ACTION NETWORK

- Aim: To determine frequency of appropriate PERT use in pancreatic cancer & impact on symptom alleviation
- Methods: Survey based study of patients in the Pancreatic Cancer Action Network's Patient Registry of 25 questions about their experience with PERT.
- Results:
  - 136 patients: 62 (46%) female; Median age at enrollment 63 (range 23-86)
  - 70% adenocarcinoma, 9% neuroendocrine, & 21% other/unknown
  - 85 (63%) surgery, 59 (43%) radiation therapy, & 112 (82%) chemotherapy

PERT Usage:

- 84% (115/136) spoke to a healthcare provider about PERT
- 76% (104/136) were prescribed PERT, of which 65% (68/104) were correctly prescribed PERT
- Only 44/68 reported compliance with correctly prescribed PERT (32% overall)

Barkin JA, et al. Pancreas 2019;48(6):780-6.

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Appropriate Use of PERT in Pancreatic Cancer Patients Is Low, But Improves Symptoms & Weight Loss

PANCREATIC CANCER ACTION NETWORK

Symptom Response: PERT with meals vs. prior/after meals:

- Decreased "Feeling of indigestion" (p=0.005)
- Improved "Increased or foul-smelling flatus" (p=0.04)
- Trend to less "Frequent stools," "Loose stools" & "Visible food particles in stool"
- Trend to more weight gain & less weight loss

Conclusions:

- Appropriate PERT prescriptions & compliance with PERT administration guidelines remains low
- Improvement in symptoms and less weight loss significantly correlated with appropriate use of PERT
- Increase in PC patient and provider education about appropriate PERT usage and administration is warranted

Barkin JA, et al. Pancreas 2019;48(6):780-6.

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Real-World Challenges to PERT Therapy

- Real-world patient experience survey-based study of 75 members of Inspire's Pancreatitis or Pancreatic Cancer support communities with EPI, with acute pancreatitis, chronic pancreatitis, pancreatic cancer, or pancreatic surgery, with current/past PERT use.

Key Survey Findings:

- Healthcare provider provided detailed information about EPI: 54%
- Healthcare provider provided detail information about how PERT works to treat EPI: 56%
- 83% searched for information about EPI
- 56% were taking PERT solely before or after eating
- 36% reported taking suboptimal PERT doses
- 39% reported no follow-up
- 24% decreased their PERT dosage without consulting their physician
- 21% reported purposely skipping PERT.

1. Barkin JA, et al. Pancreas 2024;53(1):e16-e21.

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PERT Use in Chronic Pancreatitis and Pancreatic Cancer Remains Suboptimal

- Nationwide analysis to evaluate appropriate use of PERT in chronic pancreatitis and pancreatic cancer patients
- 37,061 Chronic pancreatitis & 32,461 pancreatic cancer patients of 48.67 million enrollees in the PharMetrics claims database
- Appropriate PERT use: daily dose of >120,000 lipase units/day.

	Chronic Pancreatitis	Pancreatic Cancer
Tested for EPI	6.5%	1.9%
Filled Rx for PERT	30.4%	21.9%
Prescribed Appropriate PERT dose	8.5%	5.5%

- Predictors of PERT use: Number of comorbidities, Testing for EPI, Pancreatic surgery, Duration of enrollment

Forsmark CE, et al. Aliment Pharmacol Ther. 2020;51(10):958-967.

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Pancreatic Cancer-Associated EPI Disparities

- Aim: Investigate prevalence of EPI treatment with PERT in Pancreatic Cancer (PC) and factors influencing treatment
- Methods: Case control study of PC pts identified using SNOMED-CT coding with and without PERT rx in commercial health record database (Explorys, Inc, Cleveland, OH, USA) using logistic regression.

More Likely to Receive PERT Rx	Less Likely to Receive PERT Rx
Caucasian (OR 1.693, p<0.0001)	African-American (OR 0.7281, p<0.0001)
Age < 65 (OR 1.204, p<0.0001)	
Non-smoker (OR 2.6894, p<0.0001)	
Cannabis user (OR 2.067, p<0.0001	
Hx of Chronic Pancreatitis (OR 2.9572, p<0.0001)	
Malnutrition (OR 2.4592, p<0.0001)	
Hx of Bariatric Surgery (OR 2.1705, p<0.0001)	
Vitamin D Deficiency (OR 2.057, p<0.0001)	

- PC Prevalence: 58,530 of 64,213,430 pts (0.09%)
- PERT Rx Prevalence: 5,540 of 58,530 pts (9.47%)
- Conclusion: EPI in PC remains undertreated, disproportionately affecting older and African-American patients

Chittajallu V, …Barkin JA, et al. ACG 2020 Abstract S0005. *Am J Gastroenterol.* 2020;115(SUPPL):s2-3.

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Disparities in Chronic Pancreatitis-Associated EPI

- Aim: Investigate prevalence of EPI treatment with PERT in Chronic Pancreatitis (CP) and factors influencing treatment
- Methods: Case control study of CP pts identified using SNOMED-CT coding with and without PERT rx in commercial health record database (Explorys, Inc, Cleveland, OH, USA) using logistic regression.

More Likely to Receive PERT Rx	Less Likely to Receive PERT Rx
Caucasian (OR 1.55, p<0.0001)	African-American (OR 0.76, p<0.0001) Hispanic (OR 0.91, p<0.01)
Tobacco Smoker, Cannabis User (p<0.0001)	• CP Prevalence: 96,960 of 64,213,430 pts (0.15%) • PERT Rx Prevalence: 13,540 of 96,960 pts (14.0%) • Conclusion: EPI in CP remains undertreated, with significant treatment disparities affecting African-American and Hispanic patients
Hx of Pancreatic Cancer (OR 1.83, p<0.0001)	
Vitamin D Deficiency (OR 1.68, p<0.0001)	
Osteoporosis (OR 1.46, p<0.0001)	
Malnutrition (OR 1.96, p<0.0001)	
Hx of Bariatric Surgery (OR 1.40, p<0.0001)	
Hx of Celiac Disease (OR 1.50, p<0.0001)	

Chittajallu V, …Barkin JA, et al. APA 2020 Abstract. *Pancreas*. 2020;49(10):1402-3.

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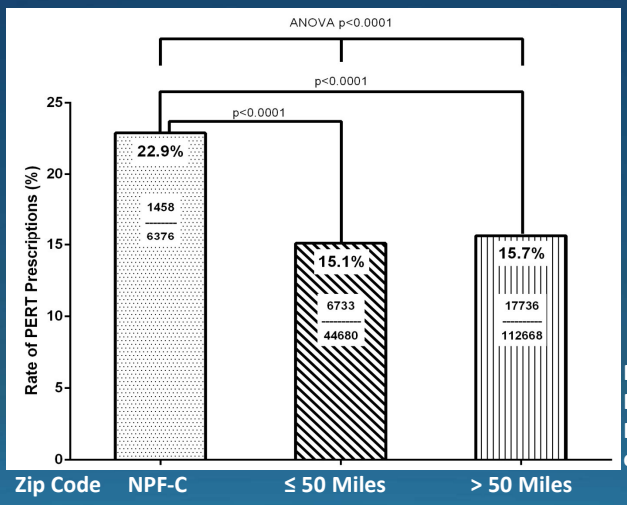
Pancreatic Specialty Centers Have Improved Rates of Treatment of EPI in Chronic Pancreatitis

The National Pancreas Foundation



Overall EPI Treatment Rate 15.8% Nationwide

NPF-C: National Pancreas Foundation Center of Excellence

Barkin JA, et al. *Pancreas*. 2018;47(10):1373

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PERT Use in Unresectable Pancreatic Cancer

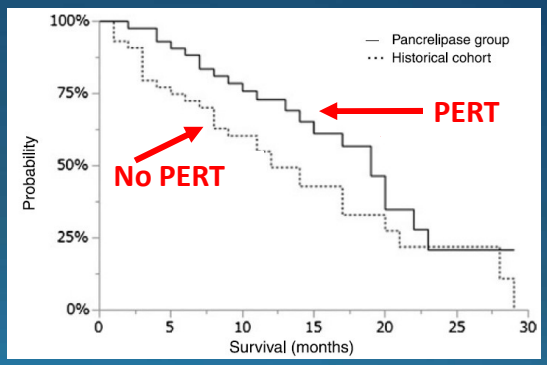
- Aim: Assess the effect of PERT use on BMI in unresectable Pancreatic Cancer
- Methods: open label RCT of PERT in 88 patients in Japan with unresectable pancreatic cancer to assess BMI at 8 weeks (1ry endpoint), other nutritional markers (2ry), and survival (2ry)

Results:

- Change in BMI at 8 weeks: No significant difference (p=0.780)
- Other nutritional markers comparable in PERT vs. no PERT

Survival:

- **Median Overall Survival**: PERT 19 months (95%CI 14-22mon) vs. No PERT 12 months (95%CI 8-17mon) (p=0.070)
- **1-Year Survival**: PERT 73.0% vs. No PERT 49.4%



Saito T, et al. Pancreas 2018;47(7):800-6

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Development of Diabetes After Acute Pancreatitis

- Systematic review/meta-analysis of 31 studies of 13894 pts[1]
- Pooled DM incidence: 23% (95% CI 16-31%); 15% insulin dependent (95% CI 9-23%)
- Risks factors of DM after AP:
  - Severe AP vs. Mild AP (39 vs 14%)
  - Presence of necrosis (37 vs 11%)
  - Alcoholic vs. Biliary AP (28 vs 12%)
- Pooled rate of DM increases with time (20% at < 5yrs; 37% at > 5 yrs)
- Pooled rate of insulin use increases with time (14% at < 5 years; 25% at > 5 yrs)
- Post-AP DM increases risk of mortality and hospitalization compared to traditional DM type 2 in a matched (10:1 matching ratio) nationwide population-based cohort study of 959 patients from New Zealand[2]

1. Zhi M, et al. Front Physiol. 2019 May 31;10:637.
2. Cho J, et al. Am J Gastroenterol 2019;114(5):804-12.

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Epidemiology and Pathogenesis of Diabetes in Chronic Pancreatitis

- Diabetes from Pancreatic disease = Pancreatogenic Diabetes = Type 3c diabetes mellitus
- Diabetes in CP: Prevalence 30-40%[1,2], Overall Incidence 30%[3]
- Progressive Incidence: 15% (3 yrs) → 33% (5+ yrs) → 46-83% (20+ yrs) → >90% (50+ yrs)[3-6]
- Risk Factors: overweight/obese, adult onset of CP, EPI, pancreatic surgery, calcifications in pancreas, duration of CP[1,2,7,8]
  - Effect of Alcohol? Mixed data, no increased risk on meta-analysis[3]

1. Bellin MD, et al. Am J Gastroenterol 2017;112:1457-65.
2. Schwarzenberg SJ, et al. Gastroenterol Nutr 2019;68:566-73.
3. Zhu X, et al. Pancreas 2019;48:868-75.
4. Pan J, et al. Medicine (Baltimore) 2016;95:e3251.
5. Malka D, et al. Gastroenterology 2000;119:1324-32.
6. Wang W, et al. Pancreas 2011;40:206-12.
7. Aslam M, et al. Pancreatology 2021;21:15-20.
8. Olesen SS, et al. UEGJ 2020;8:453-61.

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Treatment Challenges and Screening for Diabetes in Chronic Pancreatitis

- *Remember*: New onset diabetes with weight loss → evaluate for pancreatic cancer
- Challenging to treat given alpha cell (glucagon) and beta cell (insulin) dysfunction with more rapid insulin dependence than type 2 DM[1]
  - Reduced insulin secretion early on in CP before development of advanced CP morphology[2]
  - Brittle diabetes, more prone to hypoglycemic episodes
  - Not an ideal medication regimen
- Screening for diabetes in CP: not mentioned in 2020 ACG CP guidelines[3]
- Consider Hemoglobin A1c testing on an annual basis

1. Woodmansey C, et al. Diabetes Care 2017;40:1486-93.
2. Lundberg R, et al. Pancreas 2016;45:565-71.
3. Gardner TB, et al. Am J Gastroenterol 2020;115:322-39.

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Effects of Diabetes in Chronic Pancreatitis

- COSMOS Study compared Type 2 DM with Diabetes in CP[1,2]:
  - Similar risks of hospitalization or mortality from MI, peripheral vascular disease, cerebrovascular disease
  - Diabetes in CP → ↑ risk of hospitalization from COPD (HR 1.7), infectious disease (HR 1.4), mod-sev renal disease (HR 1.4), all-cause mortality (HR 1.3)
- ↑ Risk of Pancreatic Cancer in CP with diabetes vs CP without diabetes[3-5]
  - Baseline ↑ risk of Pancreatic Cancer in CP vs general population
  - ↑ Cancer-related mortality in women with diabetes in CP vs type 2 DM or type 1 diabetes[1]
  - COSMOS Study: Compared to Type 2 DM alone, ↑ Pancreatic cancer risk in CP without and with diabetes (Without aHR 4.9; With aHR 12) → *CP and Diabetes are compounding risks for Pancreatic Cancer*[5]
- PROCEED Study: ongoing prospective study to evaluate CP and complications including diabetes[6]

1. Cho J, et al. Acta Diabetol 2021;58:797-807.
2. Cho J, et al. Am J Gastroenterol 2019;114:804-12.
3. Munigala S, et al. Dig Dis Sci 2022;67:708-15.
4. Liao KF, et al. Taiwan J Gastroenterol Hepatol 2012;27:709-13.
5. Cho J, et al. Diabetes Care 2020;43:2106-12.
6. Yadav D, et al. Pancreas 2018;47:1229-38.

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Case Wrap-Up

- Treatment for EPI with PERT was started
- Bloating and abdominal pain improved
- Steatorrhea resolved
- He gained back 5 pounds
- Vitamin D supplemented and normalized
- CA 19-9 remains normal
- He remains in an active imaging screening program for pancreatic cancer
- He is following with endocrinology for management of diabetes

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Take Home Points

- EPI is common in Chronic Pancreatitis as well as other diseases
- EPI may present with increased stool frequency and decreased stool consistency amongst other maldigestive symptoms
- EPI is treated with PERT
- Untreated EPI has substantial impact on symptoms, quality of life, morbidity, and mortality
- Diabetes is common in pancreatic disease, is different than traditional type 2 Diabetes, and confers unique risks to the patient

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Questions

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