NCSG Annual Conference 2023

Treatment of Chronic Pancreatitis

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DISCLOSURES

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MEDICAL PROGRESS

CHRONIC PANCREATITIS

MICHAEL L. STEER, M.D., IRVING WAXMAN, M.D.,
AND STEVEN FREEDMAN, M.D.

IN 1788 Cawley reported on a "free living young man" who had died of emaciation and diabetes and whose postmortem examination revealed multiple pancreatic calculi.[1] In the two centuries since that early description of chronic pancreatitis, literally thousands of reports dealing with this disease have been published, yet chronic pancreatitis remains an enigmatic process of uncertain pathogenesis, unpredictable clinical course, and unclear treatment.

ACG Clinical Guideline: Chronic Pancreatitis

Timothy B. Gardner, MD, MS, FACG[1], Douglas G. Adler, MD, FACG[2], Chris E. Forsmark, MD, FACG[3], Bryan G. Sauer, MD, MSc (Clin Res), FACG (GRADE Methodologist)[4], Jason R. Taylor, MD[5] and David C. Whitcomb, MD, PhD, FACG[6]

Chronic pancreatitis (CP) is historically defined as an irreversible inflammatory condition of the pancreas leading to varying degrees of exocrine and endocrine dysfunction. Recently however, the paradigm for the diagnosis has changed in that it breaks with the traditional clinicopathologic-based definition of disease, focusing instead on diagnosing the underlying pathologic process early in the disease course and managing the syndrome more holistically to change the natural course of disease and minimize adverse disease effects. Currently, the most accepted mechanistically derived definition of CP 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. The most common symptom of CP is abdominal pain, with other symptoms such as exocrine pancreatic insufficiency and diabetes developing at highly variable rates. CP is most commonly caused by toxins such as alcohol or tobacco use, genetic polymorphisms, and recurrent attacks of acute pancreatitis, although no history of acute pancreatitis is seen in many patients. Diagnosis is made usually on cross-sectional imaging, with modalities such as endoscopic ultrasonography and pancreatic function tests playing a secondary role. Total pancreatectomy represents the only known cure for CP, although difficulty in patient selection and the complications inherent to this intervention make it usually an unattractive option. This guideline will provide an evidence-based practical approach to the diagnosis and management of CP for the general gastroenterologist.

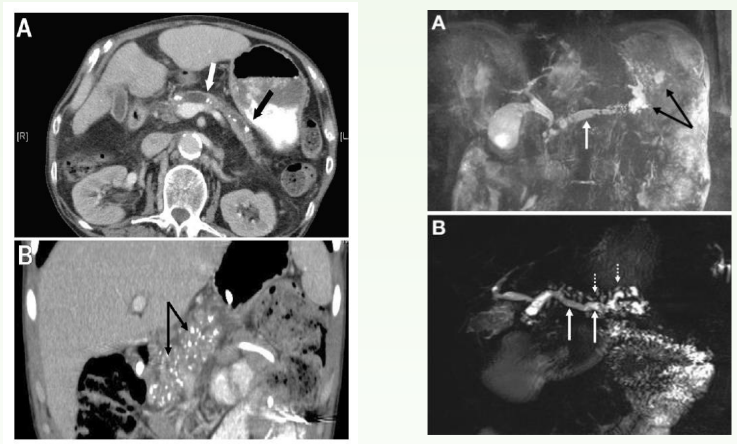
Am J Gastroenterol 2020;115:322–339. https://doi.org/10.14309/ajg.0000000000000535; published online February 5, 2020

Gardner T, et al. AJG 2020

CLINICAL GUIDELINES

ACG Clinical Guideline: Chronic Pancreatitis

Timothy B. Gardner, MD, MS, FACG[1], Douglas G. Adler, MD, FACG[2], Chris E. Forsmark, MD, FACG[3], Bryan G. Sauer, MD, MSc (Clin Res), FACG (GRADE Methodologist)[4], Jason R. Taylor, MD[5] and David C. Whitcomb, MD, PhD, FACG[6]



Gardner T, et al. AJG 2020

DIAGNOSIS

- Question: Should **cross-sectional imaging** (CT or MRI) or **EUS** be used to diagnose CP in all patients suspected of having CP?
- Question: Should **s-MRCP** vs non–secretin-enhanced MRCP be used to make the diagnosis of CP?
- Question: Should **direct vs indirect pancreatic function tests** be used to make the diagnosis of CP?
- Question: Should **pancreatic histology** vs imaging be used to make the diagnosis of CP?

Clinical Review & Education

JAMA | Review

Diagnosis and Management of Chronic Pancreatitis
A Review

Vikesh K. Singh, MD, MSc; Dhiraj Yadav, MD, MPH; Pramod K. Garg, MD

DIAGNOSTIC TESTS

Table 3. Sensitivity, Specificity, Advantages, and Disadvantages of Diagnostic Tests for Chronic Pancreatitis

Diagnostic Study	Findings	% (95% CI)[a] Sensitivity	Specificity	Advantages	Disadvantages	Recommendation
CT	Calcifications, marked ductal dilation, atrophy,	75 (66-83)	91 (81-96)	High sensitivity for calcifications High sensitivity for diagnosing CP complications	Suboptimal visualization of pancreatic duct Low sensitivity and specificity for early CP	First-line diagnostic imaging study, best for calcification and marked dilation of the pancreatic duct
MRI with MRCP with or without secretin	Parenchymal changes (atrophy, T1 signal intensity) Ductal changes (main pancreatic duct dilation, stricture or irregularity as well presence of abnormal side branches) Secretin during MRCP stimulates pancreatic secretion, which causes duodenal filling that can be assessed quantitatively for exocrine function	78 (69-85)	96 (90-98)	Secretin-enhanced MRCP has higher sensitivity and specificity than CT for changes of the main pancreatic duct including dilation and strictures as well as changes in the side branches No ionizing radiation	Low sensitivity for small ductal calculi and parenchymal calcifications Lack of widespread availability	If CT shows normal results but suspicion of CP is high, MRI with MRCP should be obtained to evaluate for ductal changes
EUS	Four parenchymal criteria (lobularity, cyst, hyperechoic foci, and hyperechoic strands) Five ductal criteria (dilation, irregularity, calcifications or stones, echogenic duct wall margins, and side branch)	81 (70-89)	90 (82-95)	High sensitivity Less invasive than ERCP Allows for tissue sampling	Low specificity High interobserver variability Not all criteria carry similar importance	If CT and MRI are normal and the suspicion for CP is still high, especially in patients with RAP, EUS should be performed

Abbreviations: CP, chronic pancreatitis; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; RAP, recurrent acute pancreatitis.

[a] Sensitivity and specificity for CT, MRI-MRCP, and EUS were adopted from Issa et al.[76]

Singh V, et al. JAMA 2019

ORIGINAL ARTICLE

Diagnosis of Chronic Pancreatitis Incorporating Endosonographic Features, Demographics, and Behavioral Risk

Linda S. Lee, MD, Ying P. Tabak, PhD,† Vivek Kadiyala, MD,* Xiaowu Sun, PhD,† Shadeah Suleiman, BS,* Richard S. Johannes, MD,*† Peter A. Banks, MD,* and Darwin L. Conwell, MD‡*

TABLE 2. Comparison of Patient Characteristics From 2 Centers

Variable	Center 1 (n = 114)	Center 2 (n = 62)	*P*
Age, median (IQR), y	49.5 (39–57)	47 (35–56)	0.42
Female, n (%)	68 (59.6)	39 (62.9)	0.67
Peak bicarbonate, median (IQR)	78 (62–88)	84 (64–90)	0.20
Peak bicarbonate <75 mEq/L, n (%)	48 (42.1)	21 (33.9)	0.38
EUS score, mean (SD)	2.9 (1.5)	2.6 (2.4)	0.24

TABLE 3. Prediction Model for Abnormal ePFT and Weighted Risk Score

Parameter	All Patients (n = 176), n (%)*	Abnormal ePFT (n = 69), n (%)†	Model Coefficient	*P*	Risk Score‡
Behavior (current or previous smoking/alcohol use)					
None	76 (43)	18 (24)	Reference	N/A	0
Smoking *or* alcohol status	65 (37)	29 (45)	0.39	0.35	2
Smoking *and* alcohol status	35 (20)	22 (63)	0.76	0.15	4
No. of parenchymal abnormalities present (cysts, strands, hyperechoic foci, and lobularity)					
0	29 (16)	4 (14)	Reference	N/A	0
1 or 2	112 (64)	43 (38)	1.05	0.10	6
3 or 4	35 (20)	22 (63)	1.46	0.05	8
No. of ductal abnormalities present (irregular MPD, dilated MPD, and dilated side branches)					
0	124 (70)	34 (27)	Reference		0
1	23 (13)	9 (39)	0.19	0.71	1
2 or 3	29 (16)	26 (90)	2.14	0.002	11
Calcifications					
No	154 (88)	49 (35)	Reference	N/A	0
Yes	22 (13)	20 (91)	1.79	0.03	9

*Column % does not necessarily add to 100 because of rounding.
†Row %.
‡Risk score was calculated by dividing each variable coefficient by the smallest coefficient in the model and rounding the ratio to the integer.
N/A indicates not applicable.

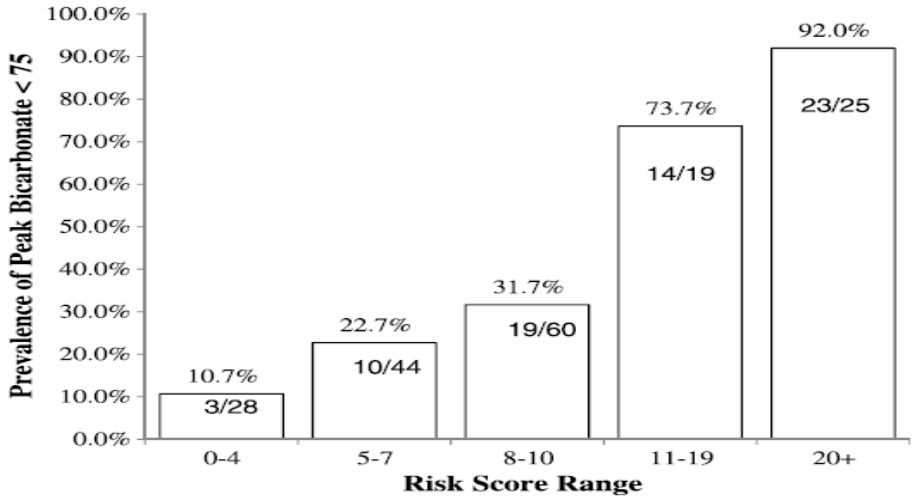
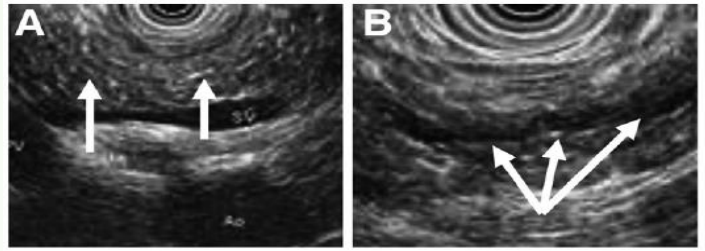
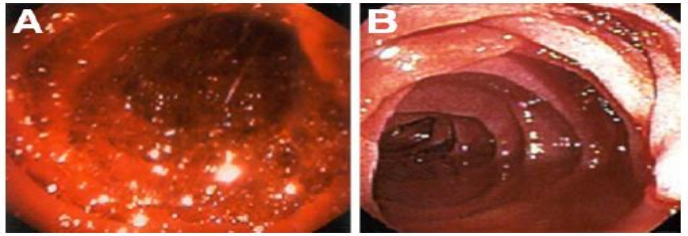


FIGURE 1. Risk score strata and associated abnormal ePFT rates.





Lee, L, Pancreas 2017

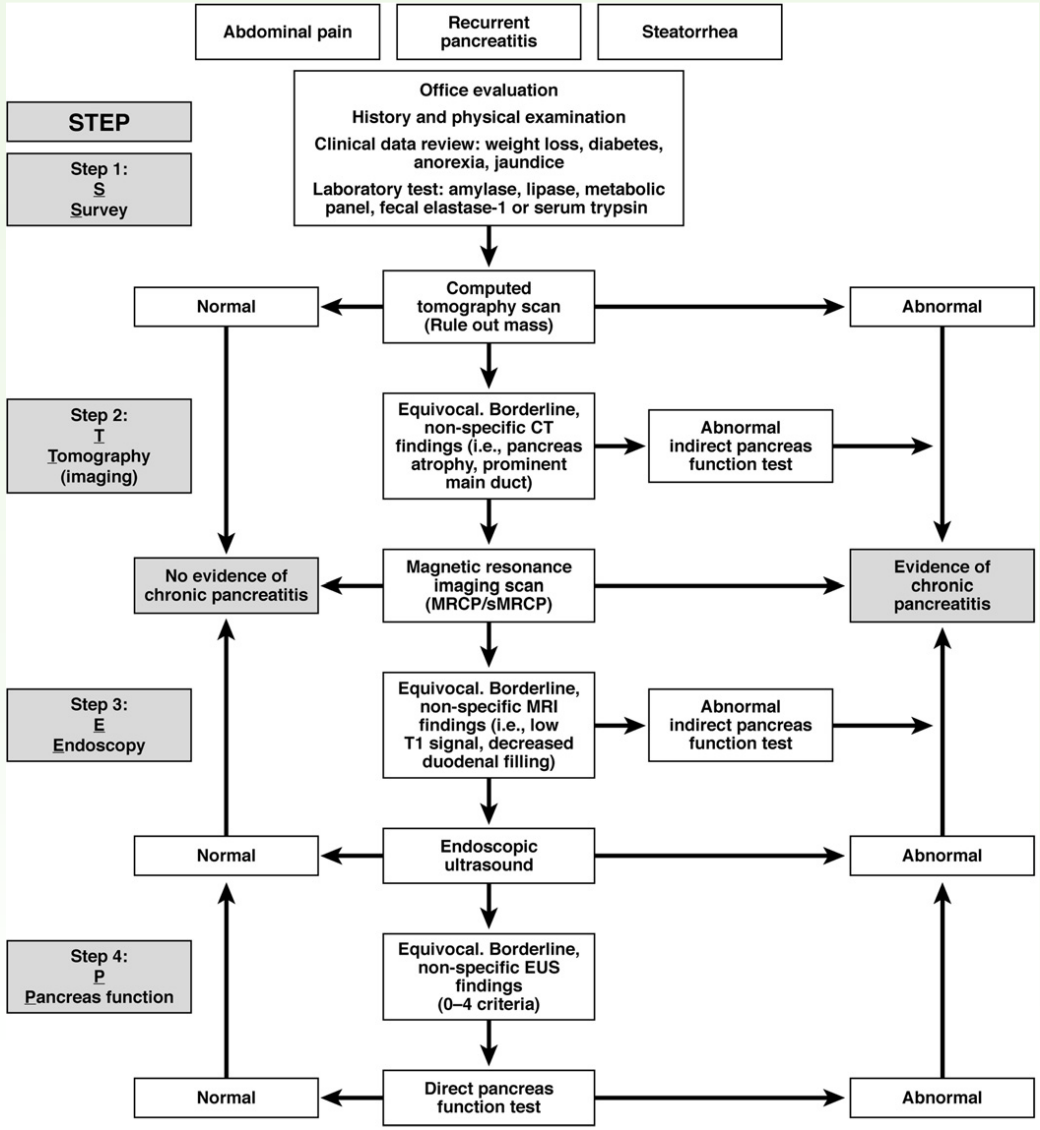
STEP-wise APPROACH

Chronic Pancreatitis: Making the Diagnosis

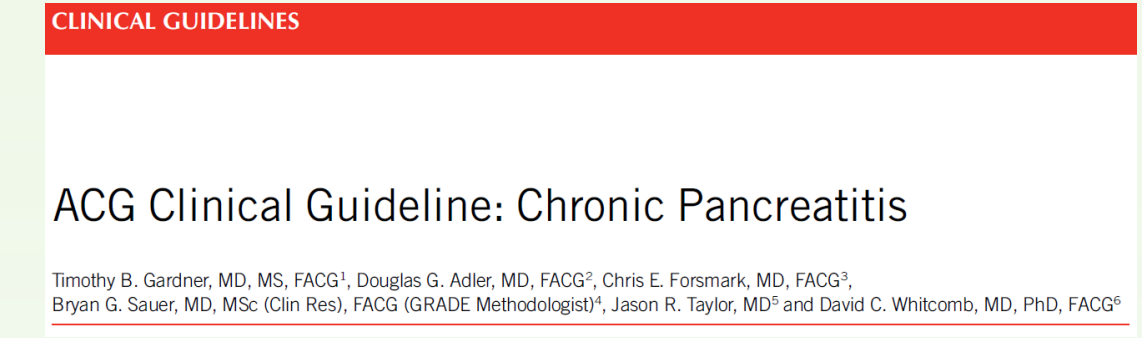
DARWIN L. CONWELL and BECHIEN U. WU

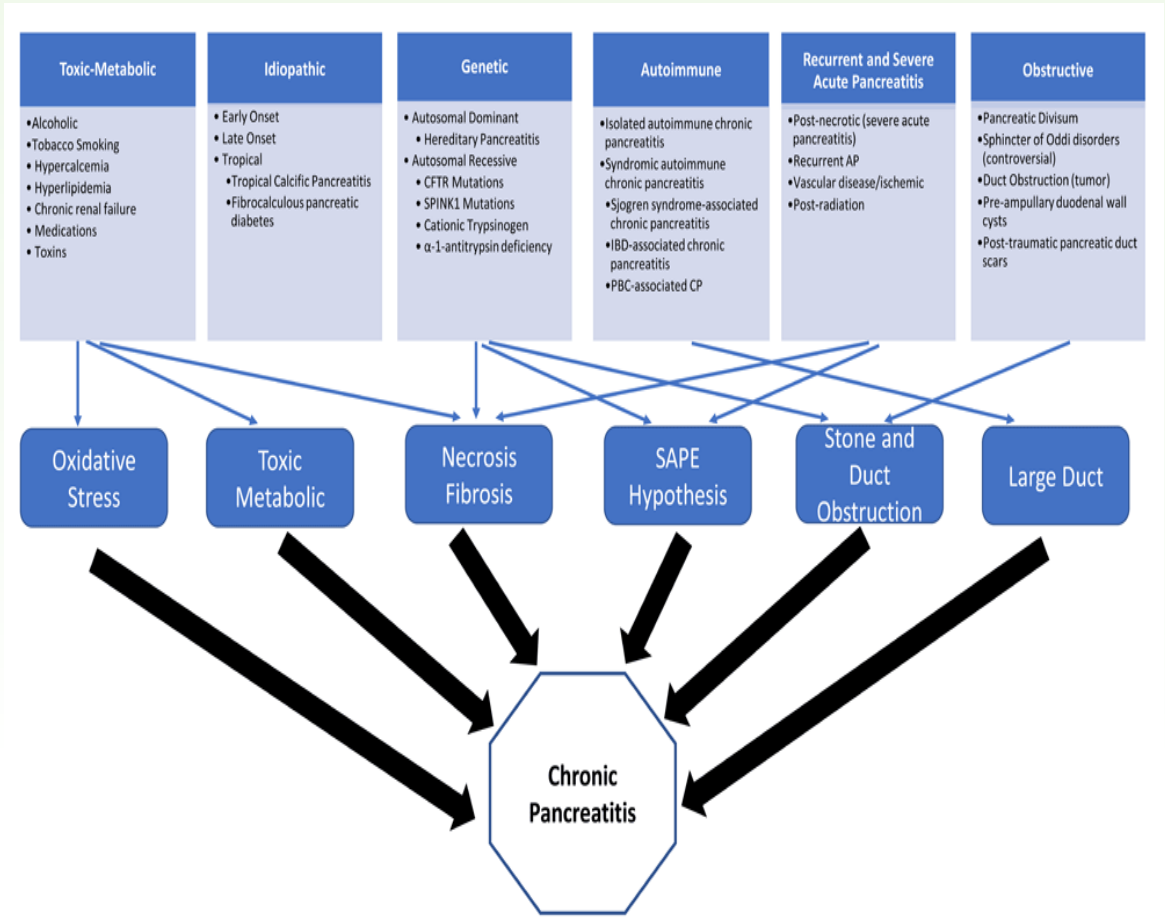
Center for Pancreatic Disease, Brigham and Women's Hospital, Division of Gastroenterology, Hepatology and Endoscopy, Harvard Medical School, Boston, Massachusetts

Conwell D and Wu B. CGH 2012



NATURAL HISTORY





- Question: Does a defined etiology vs idiopathic disease determine important clinical outcomes in CP?
- Question: Does BMI vs other etiologic factors determine the risk of developing endocrine insufficiency in CP?
- Question: Does alcohol cessation vs no alcohol cessation alter the natural history of CP?
- Question: Does tobacco cessation vs no tobacco cessation alter the natural history of CP?
- Question: Should screening examinations vs no screening examinations for pancreatic malignancy be performed in patients with CP?

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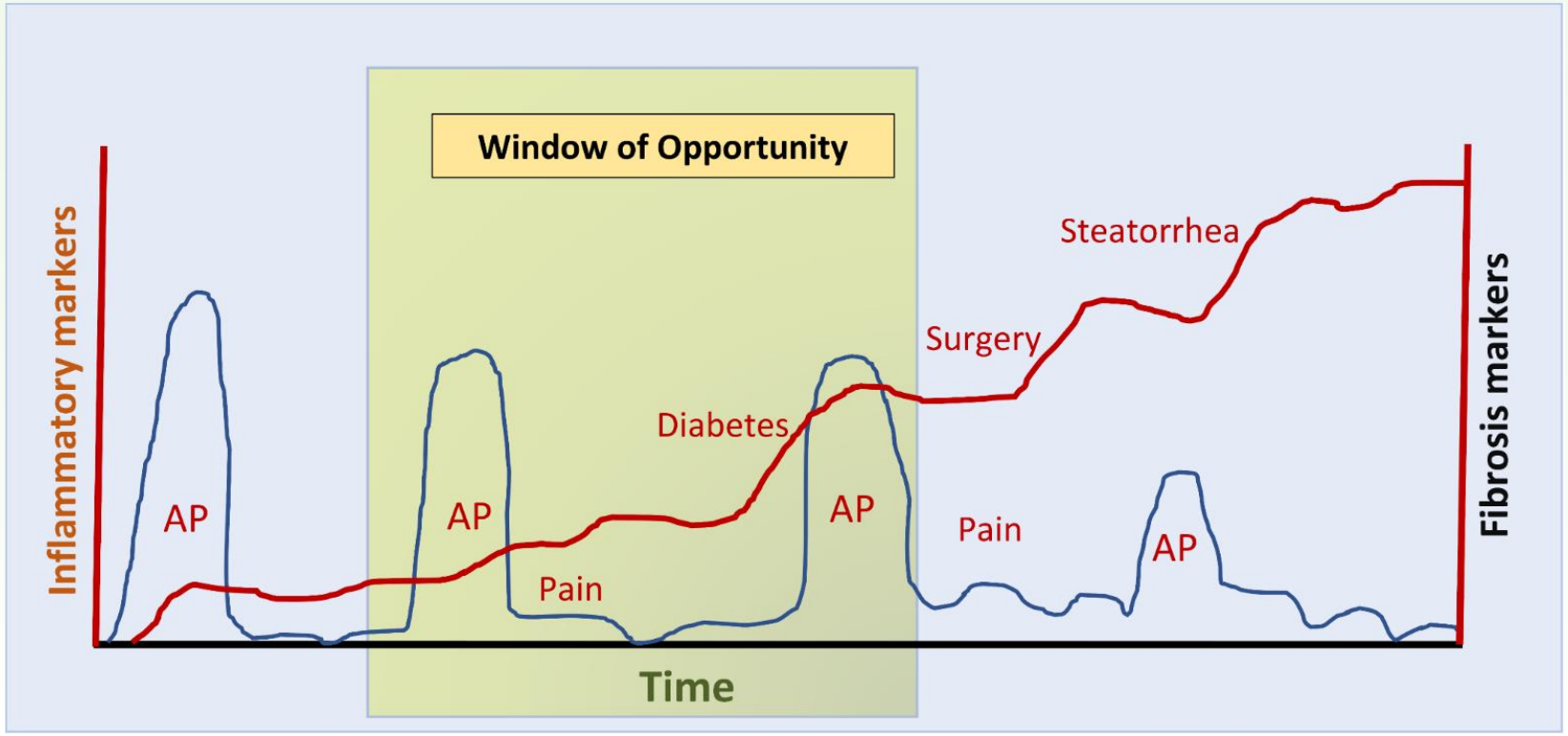
Natural History of CP



Modified from: Colombel J et al. Gastroenterology 2017;152:351-61

CLINICAL GUIDELINES

ACG Clinical Guideline: Chronic Pancreatitis

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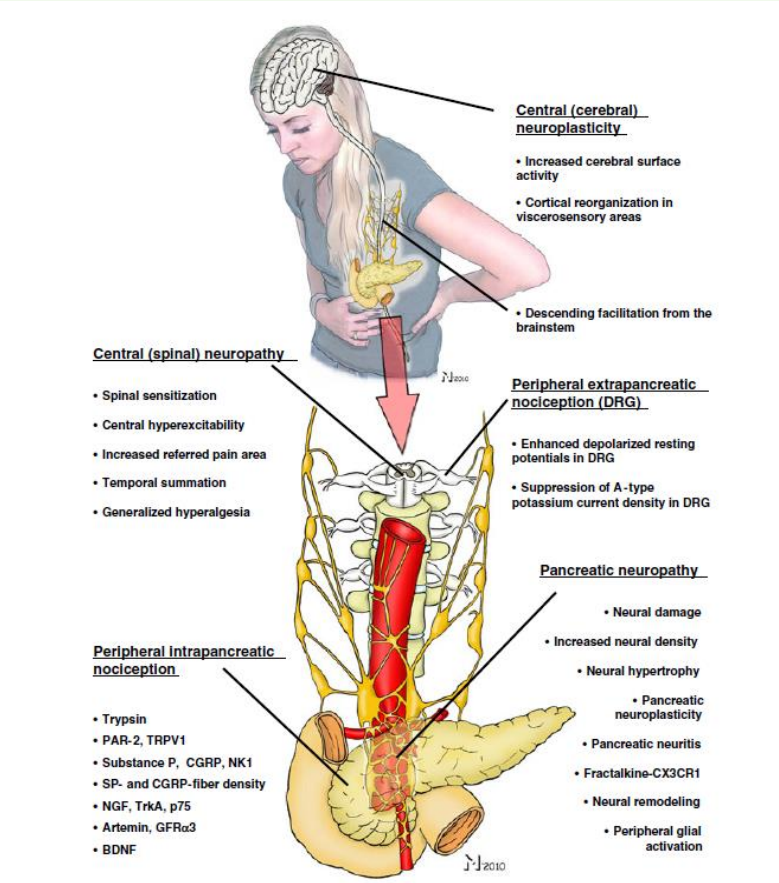

PAIN CONTROL

- Question: Should interventional **endoscopic or surgical therapy** vs no interventional therapy be used in patients with CP who are actively consuming alcohol to improve pain symptoms?
- Question: Should pancreatic duct decompression **through endoscopy vs surgery** be used in CP patients with evidence of pancreatic duct obstruction to improve pain symptoms?
- Question: Should **antioxidants** vs no antioxidants be used in patients with CP to improve pain symptoms?
- Question: Should **opiates** vs no opiates be used in patients with CP to improve pain symptoms?
- Question: Should **pancreatic enzymes** vs no pancreatic enzymes be used in patients with CP to improve pain symptoms?
- Question: Should **celiac plexus blockade** vs no celiac plexus blockade be used in patients with CP to improve pain symptoms?
- Question: Should **TPIAT vs no TPIAT** be used to treat pain symptoms in patients with CP?
- Question: Should **experimental therapeutic modalities** (i.e., radiation therapy, spinal cord stimulation, and transmagnetic brain stimulation) vs no experimental therapeutic modalities be used to treat pain symptoms in patients with CP?

Hypothetical Time-Course of Pain in Chronic Pancreatitis

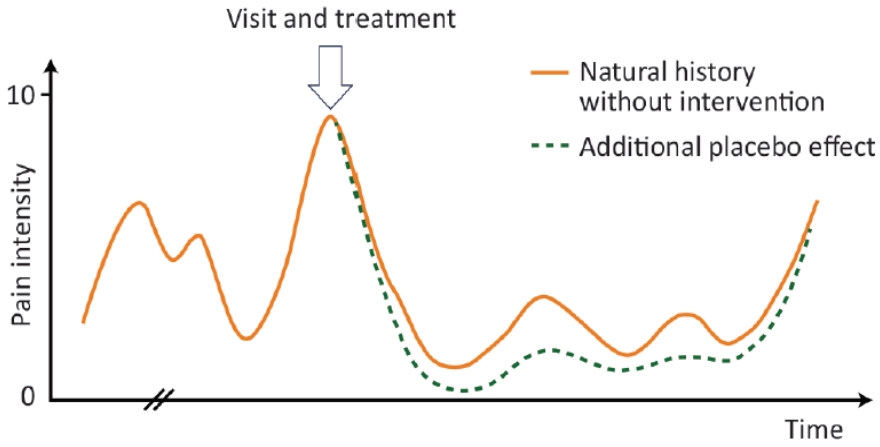

Figure 2 A hypothetical illustration of the pain intensity over time (solid curve) in a patient with chronic pancreatitis. At the initial course of disease, the pain is fluctuating and may reach a high intensity as illustrated on the y-axis. When pain intensity is the highest, the patient may be desperate and seek invasive treatment (arrow). However, the natural course of disease (in this case, the pain temporarily improves) is not taken into consideration when the outcome of uncontrolled studies of invasive treatment is evaluated. Such a selection bias necessitates a control group subjected to sham surgery/endoscopy before any definitive conclusions regarding effectiveness of treatment can be taken. The placebo effect (stippled green line) can further add to the pain relief after invasive treatments.

Drewes AM, et al. Gut 2018

Quantitative Sensory Testing

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

A clinically feasible method for the assessment and characterization of pain in patients with chronic pancreatitis

Anna Evans Phillips [a], Mahya Faghih [b], Louise Kuhlmann [c, d], Isabelle M. Larsen [c], Asbjørn Mohr Drewes [c, d], Vikesh K. Singh [b], Dhiraj Yadav [a], Søren Schou Olesen [c, d, *], On behalf of the Pancreatic Quantitative Sensory Testing (P-QST) Consortium

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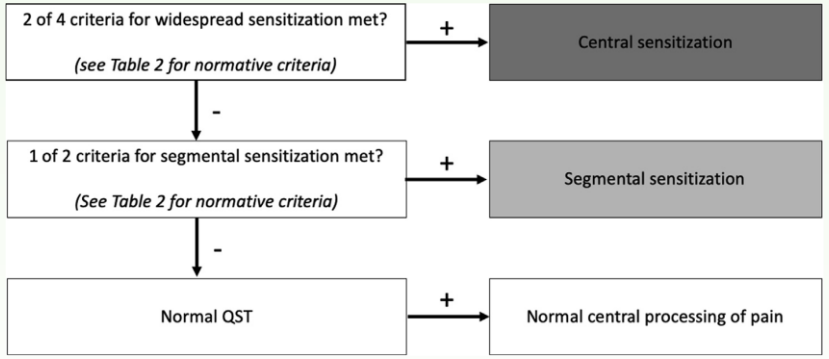
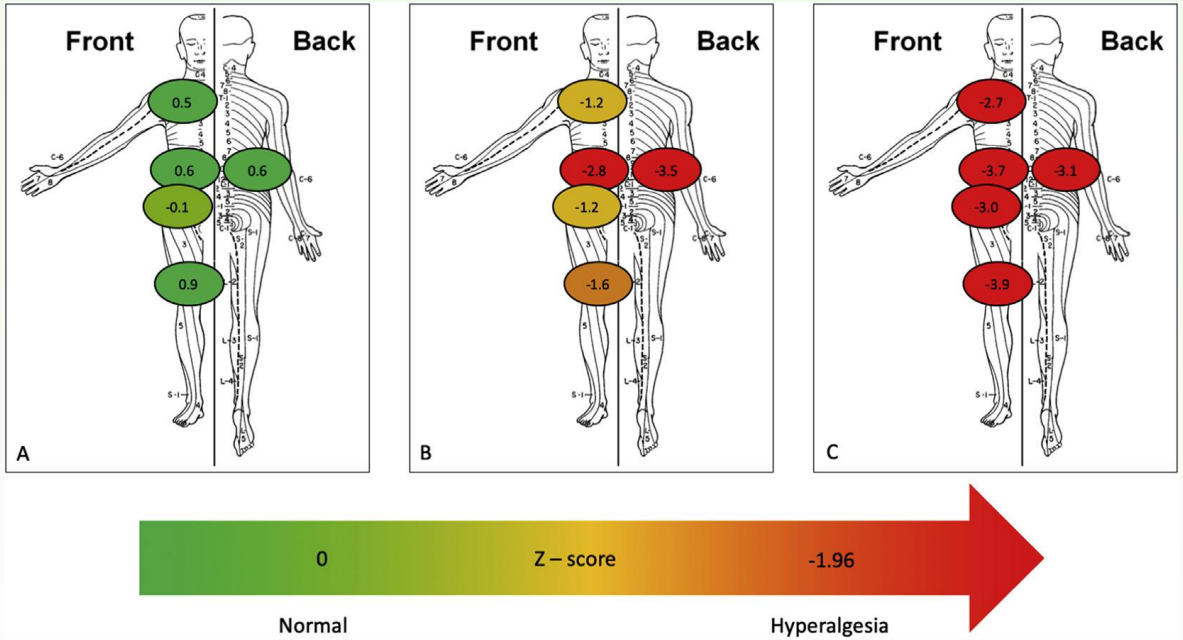
[b] Johns Hopkins University School of Medicine, Division of Gastroenterology and Hepatology, Department of Medicine, Baltimore, MD, USA
[c] Centre for Pancreatic Diseases and Mech-Sense, Department of Gastroenterology and Hepatology, Aalborg University Hospital, Aalborg, Denmark
[d] Department of Clinical Medicine, Aalborg University, Aalborg, Denmark





Conclusion: We show normative reference values for a clinically feasible method for assessment and characterization of pain mechanisms in patients with CP. Application of this method streamlines the evaluation of pancreatic pain and may be used to inform treatment.
Clinicaltrials.gov id: NCT03434392.

Psychiatric Comorbidity in Patients With Chronic Pancreatitis Associates With Pain and Reduced Quality of Life

Anna Evans Phillips, MD, MS[1], Mahya Faghih, MD[2], Asbjørn Mohr Drewes, MD, DMSc, PhD[3,4], Vikesh K. Singh, MD, MSc[2], Dhiraj Yadav, MD, MPH[1] and Søren Schou Olesen, MD, PhD[3,4], On behalf of the Pancreatic Quantitative Sensory Testing (P-QST) Consortium

RESULTS: **One hundred seventy-one patients with CP (mean age 53.8 ± 13.7 years, 60% men) were included. Anxiety and depression were present in 80 (46.8%) and 66 (38.6%) patients, with overlap in 50 (29%). Patients with anxiety or depression reported higher pain prevalence, pain severity, and pain interference scores (all $P < 0.001$). Psychiatric comorbidities also associated with reduced global health scores and functional subscales (all $P < 0.001$) and higher symptom burden ($P \leq 0.03$). An independent association was noted between global health status and depression ($P < 0.001$).**

DISCUSSION: **Psychiatric comorbidities are prevalent in patients with CP and associated with pain and QOL. Where the effect of anxiety on QOL may be mediated via pain, depression is independently related to QOL. These findings warrant consideration in the management of patients with CP.**

Am J Gastroenterol 2020;00:1–9. https://doi.org/10.14309/ajg.0000000000000782

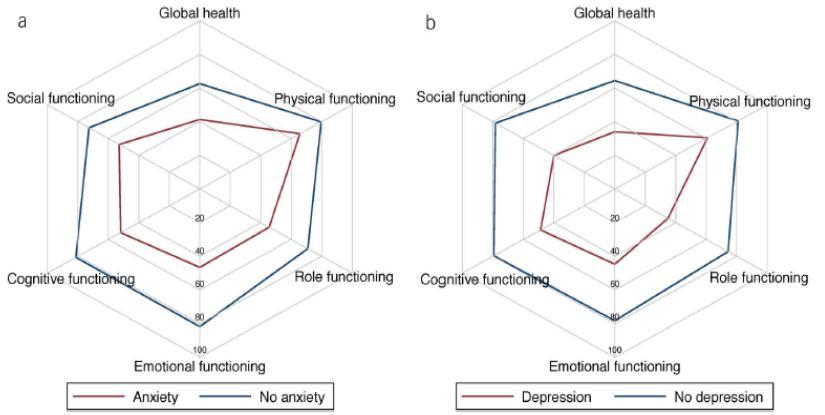


Figure 2. Comparison of EORTC-QLQ C30 global health and functioning scores between patients with and without (**a**) anxiety and (**b**) depression reveals significantly lower global health, physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning in those affected with either psychiatric comorbidity (red lines) than those without (blue lines) (all $P < 0.001$).

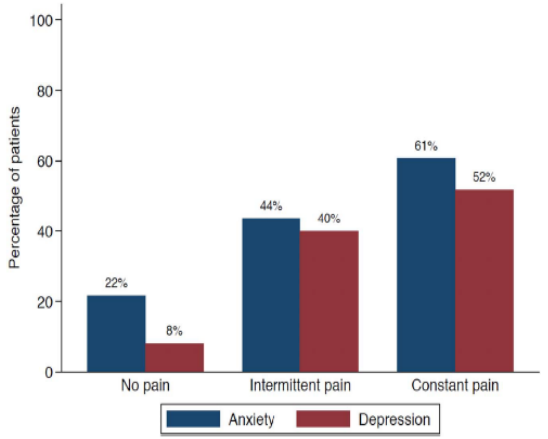
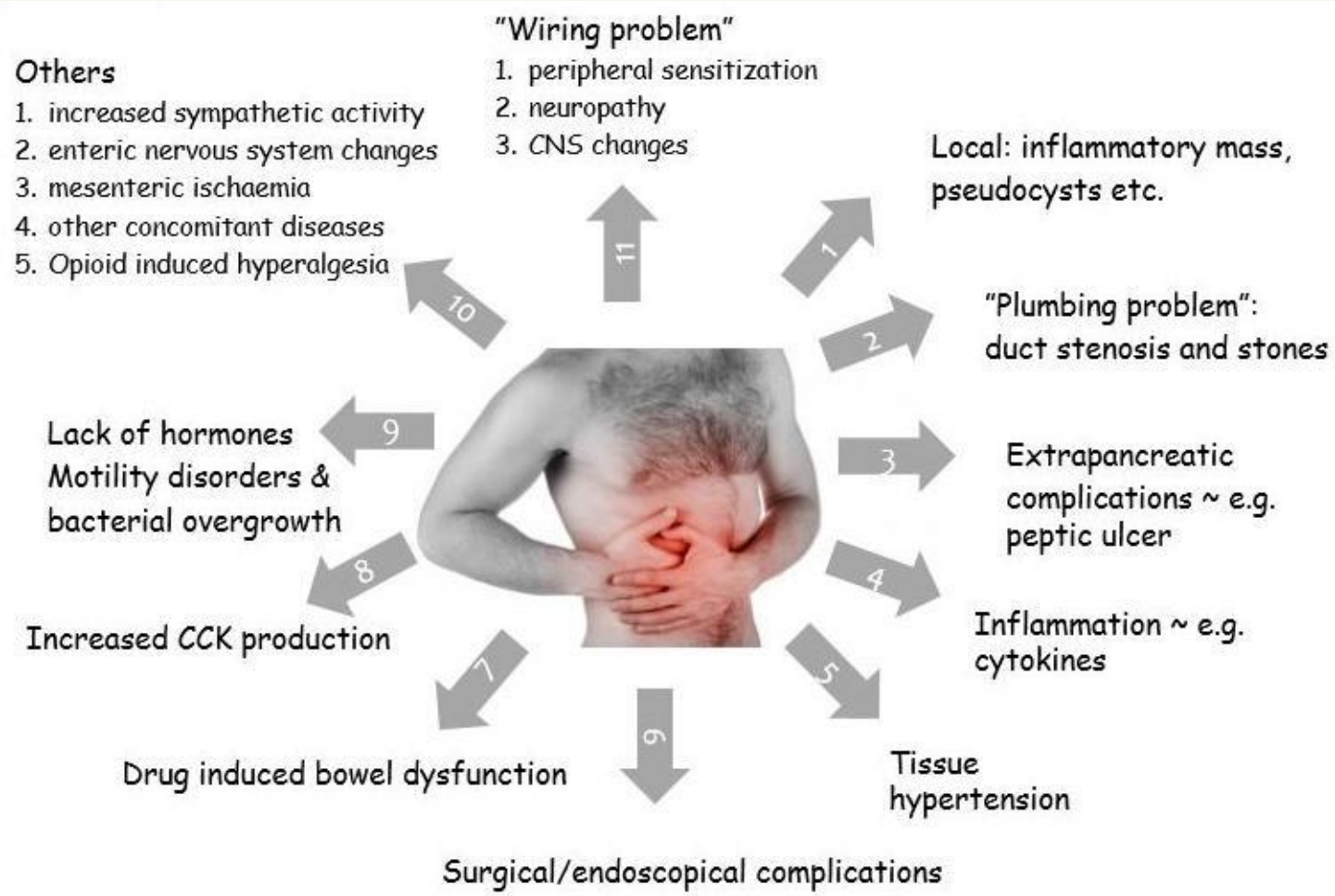
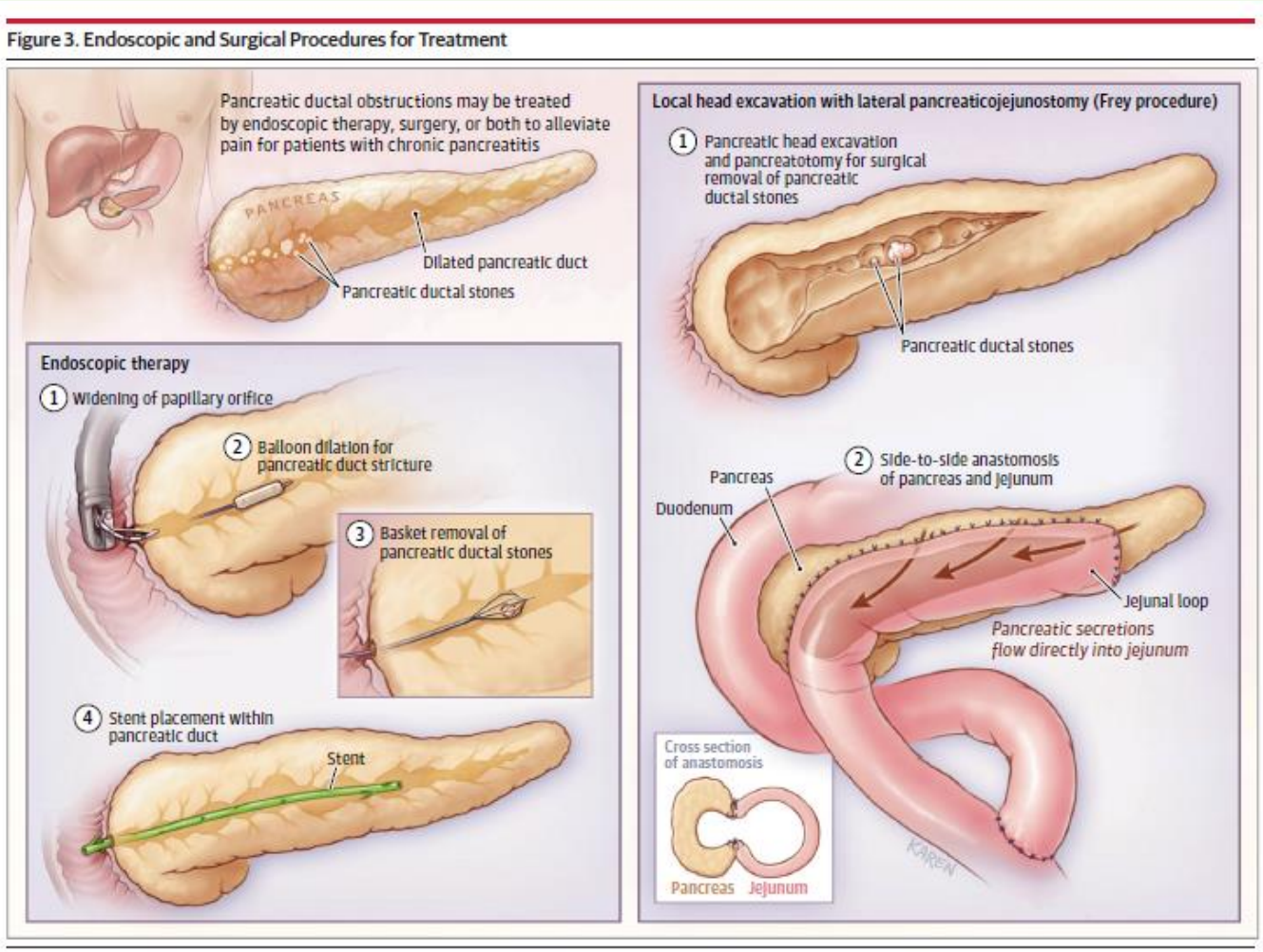


Figure 1. Prevalence of anxiety (blue) and depression (red) in patients with no pain, intermittent pain, and constant pain. Significant differences were seen between rates of both anxiety and depression in patients with intermittent or constant pain as compared to no pain (all $P = 0.001$).

Mechanism Based Approach to Chronic Pancreatitis Pain



ENDOSCOPY AND SURGERY



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ENDOSCOPY AND SURGERY

Table 4. Randomized Controlled Trials Evaluating Pain Relief of Medical and Interventional Therapies for Painful Chronic Pancreatitis

Source	No. of Patients	Comparison	Primary Outcome	Duration of Follow-up	Pain Relief	Adverse Events
Bhardwaj et al,[103] 2008	127	Antioxidants (dose: 0.54 g ascorbic acid, 9000 IU β-carotene, 270 IU α-tocopherol, 600 µg organic selenium, and 2 g methionine per d) vs placebo	Reduction in painful d/mo at 6 mo	6 mo	Reduction in mean (SD) number of painful d/mo 7.4 (6.8) vs 3.2 (4) ($P < .001$) (mainly idiopathic CP)	No significant adverse events noted except headache in 8 and constipation in 4 patients taking antioxidants (n = 71)
Siriwardena et al,[102] 2012	70	Antioxidants (dose: 2 tablets 3/d, contained 38.5 mg selenium yeast, of which 50 µg was l-selenomethionine; 113.4 mg/d α-tocopherol acetate; 126.3 mg ascorbic acid; and 480 mg l-methionine) vs placebo	Change in clinic pain score at 6 mo	6 mo	Nonsignificant reduction in pain score by 2.33 vs 1.97; $P = .50$, mainly alcoholic CP taking 85 mg of morphine/d)	No significant adverse events noted except 1 patient had diarrhea and 1 developed hepatic encephalopathy in the antioxidant group
Olesen et al,[99] 2011	64	Pregabalin (75 mg 2/d, increased to 300 mg 2/d after 1 wk) vs placebo	Change in pain intensity as measured on a visual analogue scale after 3 wk of treatment	3 wk	36% vs 24% ($P = .02$)	Four of 34 Patients in the pregabalin group had serious adverse events: pneumonia, worsening abdominal pain, eczema, and shoulder injury in 1 patient each; 35% and 24% of patients taking pregabalin reported feeling drunk and light-headedness
Talukdar et al,[108] 2016	87	Antioxidants + pregabalin vs placebo	Pain relief measured on visual analogue scale and Izbicki pain score	2 mo	48% vs 27% ($P = .04$)	Mild to moderate self-limiting nausea and vomiting in the treatment group
Dumonceau et al,[109] 2007	55	ESWL vs ERCP + ESWL	Pain relapse	2 y	58% vs 55% ($P = .63$)	3% Complication (1 patient developed pseudocyst) in the ERCP + ESWL group
Dite et al,[110] 2003	72	ERCP (no ESWL) vs surgery	Complete pain relief	5 y	15% vs 34% ($P = .002$)	8% Patients in each group had complications
Cahen et al,[111] 2007	39	ERCP + ESWL vs surgery	Complete pain relief	2 y	16% vs 40% ($P = .007$)	11 Patients (58%) had minor complications in the endoscopy group and 7 (35%) had complications in the surgery group
Cahen et al,[112] 2011	31	ERCP + ESWL vs Surgery	Complete pain relief	6.5 y (follow-up of RCT from 2007)	25% vs 53% ($P = .04$)	47% Of patients in the endoscopy group required surgery

Abbreviations: ERCP, endoscopic retrograde cholangiopancreatography; ESWL, extracorporeal shock wave lithotripsy; RCT, randomized clinical trial.

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CLINICAL GUIDELINES

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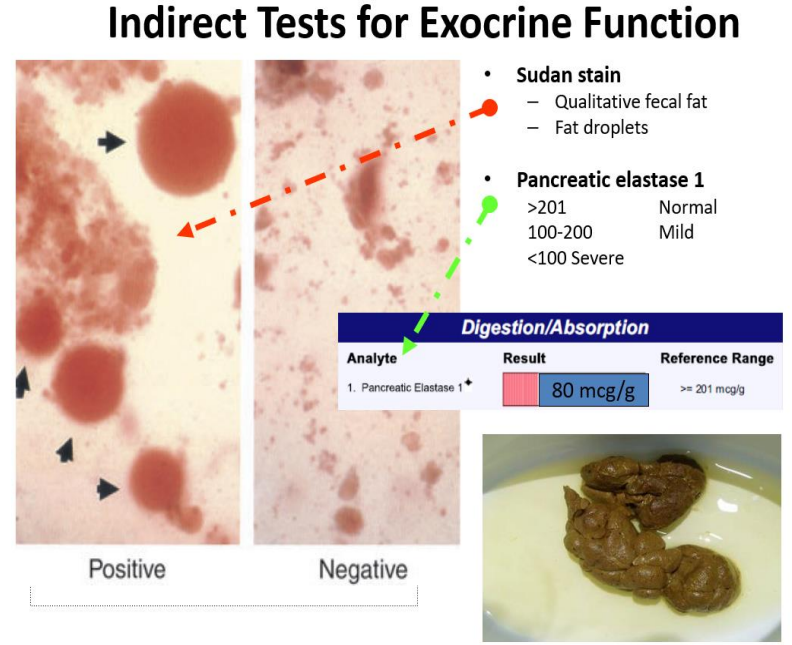
EXOCRINE INSUFFICINCY

- Question: Should **PERT vs no PERT** be used in patients with CP to improve symptoms of pancreatic insufficiency?



- Question: Should testing for **vitamin deficiency** vs no testing for vitamin deficiency be used in patients with CP and pancreatic insufficiency?

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Table 4. Test characteristics of direct and indirect pancreatic function tests (110,111)

Test	Advantages	Disadvantages
Hormonal tests of pancreatic function		
CCK stimulation test (acinar cell stimulation measuring trypsin and/or lipase)	Direct acinar cell function Detects subtle EPI	Cumbersome Not widely available Specialized laboratory testing required Patient discomfort with Dreiling tube placement 2–3 hr test
Secretin stimulation test (ductal cell stimulation measuring bicarbonate)	Direct ductal cell function Performed endoscopically Uses laboratory autoanalyzer 60 min test Measures ductal secretory ability	Not widely available Prone to measurement error Risk and cost of endoscopy
Nonhormonal tests of pancreatic function		
Fecal elastace-1	Universally available Easily obtainable Noninvasive	Moderate sensitivity Limited specificity in diarrhea Limited use in mild disease
^{13}C-mixed triglyceride test	Easily obtainable High sensitivity (90%)	Not universally available Long test duration—4–6 hr
Serum trypsinogen/trypsin	Universally available Easily obtainable Noninvasive Quantifiable for tracking function over time	Does not measure digestive tract enzymes Elevated with pancreatic pain

CCK, cholecystokinin; EPI, exocrine pancreatic insufficiency.

Sensitivity – **TP** / TP + FN - "true positive rate" – SnNouts – Rule out

Specificity – TN / TN + **FP** "true negative rate" – SpPins – Rule in

Gardner, AJG 2020

Fecal Elastase-1: Executive Summary (Remember – High False Positive Rate)

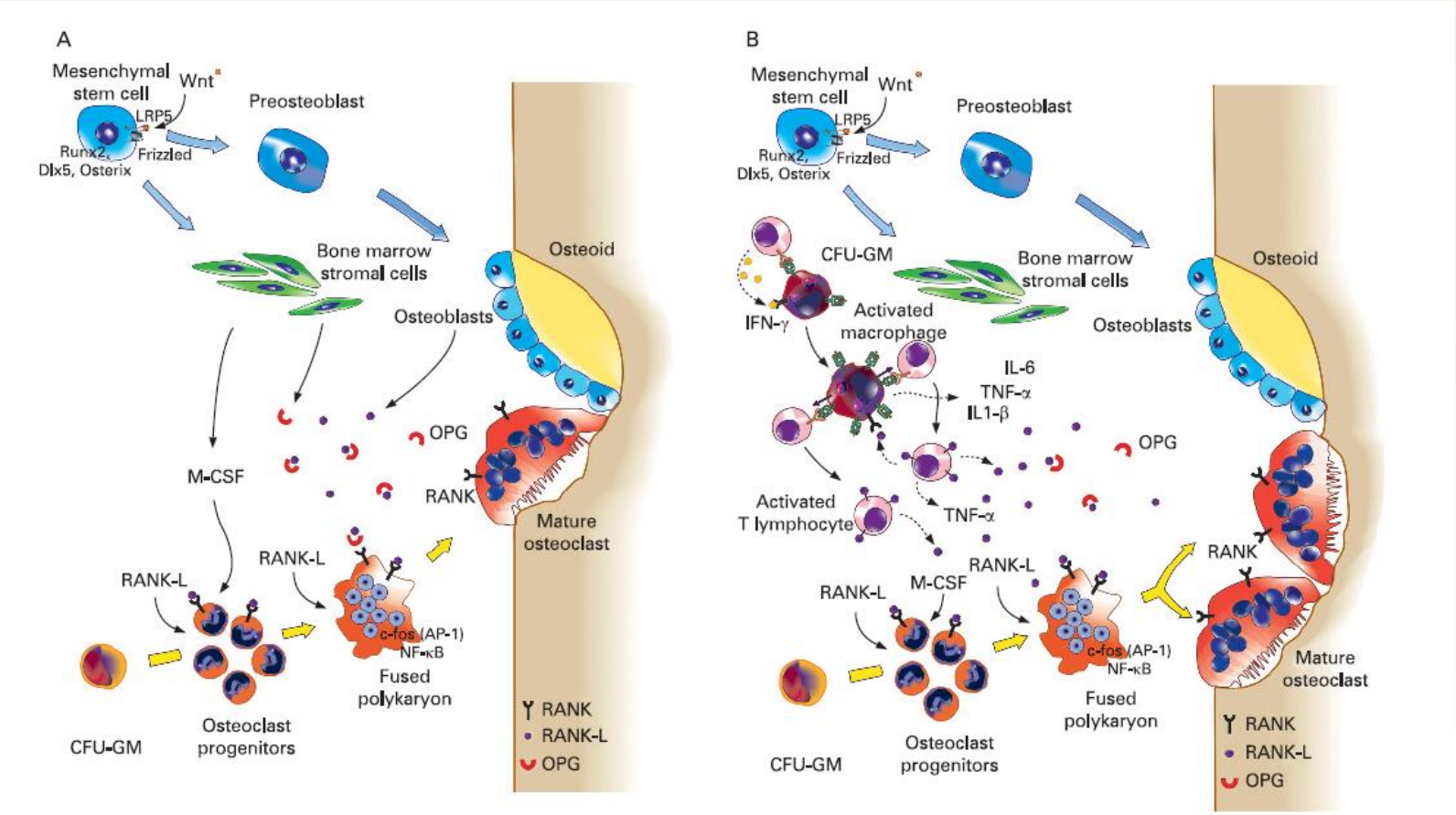
Table 1 | Studies evaluating fecal elastase-1 in settings where screening for pancreatic disease is not routine

Setting	Prevalence of abnormal fecal-elastase-1 level	Benefit of pancreatic enzyme supplementation
Celiac disease	Around 30% in patients with diarrhea[54]	One RCT reported benefit when therapy used for 3 months after diagnosis[55] One open-label study reported benefit in patients with persistent diarrhea[56]
IBS	6%[21]	One open-label study reported improved pain and stool frequency and consistency with therapy[21]
IBD	19–30%[71,72]	No treatment studies reported
HIV	23–54%[77,78,80]	Two open-label studies reported improvement in diarrhea and fat malabsorption[79,80]
Alcohol-related liver disease	7–20%[94]	No treatment studies reported.
Diabetes mellitus	Type 1, 26–44%[108–111] Type 2, 12–20%[108–110,112,113]	One RCT reported reduction in frequency of hypoglycemia[116]
Advanced renal disease	10–48%[125,126]	No treatment studies reported
Sjorgren syndrome	4% in patients with secondary Sicca syndrome[124]	No treatment studies reported
Elderly populations	11.5–20% in individuals aged 50–80 years[10,127] 1.5% in individuals >90 years[128]	No treatment studies reported

Abbreviation: RCT, randomized controlled trial.

Nature reviews | Gastroenterology & Hepatology volume 8 | July 2011

Inflammation Induces an Imbalance between Osteoclast and Osteoblast Activity



H Tilg, et al. *Gut* 2008;57:684-694

Is There a High Prevalence of Low-Trauma Fracture in Chronic Pancreatitis?

Hypothesis: Chronic Pancreatitis is a risk factor for metabolic bone disease

Aim 1: Compare prevalence of fracture

Controls

Chronic Pancreatitis

"High Risk" GI Illness

Aim 2: Compare prevalence of fracture in each "high risk" group to controls and Chronic Pancreatitis

Odds Ratio, [95% CI]

Odds Ratio of Fracture Among CP was comparable to other "High Risk" GI Disease

	Odds Ratio	95% CI
Chronic Pancreatitis	4.4	(3.7, 5.2)
Crohn's Disease **	2.6	(2.2, 3.0)
Celiac Disease	4.4	(3.4, 5.6)
Postgastrectomy	4.7	(2.8, 8.0)
Cirrhosis	4.4	(4.1, 4.7)

High Prevalence of Low-Trauma Fracture in Chronic Pancreatitis

April S. Tignor, MD, MPH[1], Bechien U. Wu, MD, MPH[1], Tom L. Whitlock, MD, MPH[1], Rocio Lopez[2], Kathryn Repas[1], Peter A. Banks, MD[1] and Darwin Conwell, MD[1]

OBJECTIVES: **Chronic pancreatitis (CP) is associated with risk factors that may negatively impact bone and mineral metabolism. The important clinical end point of osteoporosis is "low-trauma" fracture. The purpose of this study was to examine the prevalence of "low-trauma" fracture in patients with CP, compared with fracture rates in "high-risk" gastrointestinal (GI) illnesses, for which metabolic bone disease screening guidelines are in place.**

METHODS: **This is a retrospective cohort database study examining patients with CP and "high-risk" GI illnesses seen at a single tertiary care center. Time points ranged between 31 July 1998 and 31 July 2008. The main outcome measure was "low-trauma" fracture prevalence using specific International Classification of Diseases, Ninth Revision, Clinical Modification fracture codes.**

RESULTS: **A total of 3,192 CP patients and 1,461,207 non-CP patients were included in the study. The fracture prevalence (patients with fracture per total patients) was as follows: controls, 1.1% (16,208/1,436,699); Crohn's disease, 3.0% (182/6057); CP, 4.8% (154/3192); cirrhosis, 4.8% (805/16,658); celiac disease, 5.0% (74/1480); and postgastrectomy, 5.4% (17/313). Prevalence for each group was statistically greater than controls ($P<0.001$). CP fracture prevalence was greater than controls ($P<0.001$) and Crohn's disease ($P<0.001$), and comparable with the remaining "high-risk" GI illness groups ($P>0.05$). The odds of fracture (odds ratio (OR), 95% confidence interval (CI)) compared with controls, adjusted for age, gender, and race was: CP 2.4 (2.1, 2.9); Crohn's disease 1.7 (1.5, 2.0); gastrectomy 2.5 (1.5, 4.1); cirrhosis 2.6 (2.4, 2.7); and celiac disease 2.7 (2.1, 3.4). The odds of fracture for each disease group were statistically greater than controls ($P<0.0001$).**

CONCLUSIONS: **The prevalence of low-trauma fracture in CP patients is comparable with or higher than that of "high-risk" GI illnesses, for which osteoporosis screening guidelines exist.**

Am J Gastroenterol advance online publication, 24 August 2010; doi:10.1038/ajg.2010.325

Chronic Pancreatitis and Fracture

A Retrospective, Population-Based Veterans Administration Study

Satish Munigala, MD, MPH, Banke Agarwal, MD,* Andres Gelrud, MD,† and Darwin L. Conwell, MD, MS‡*

Objectives: There is increasing evidence that chronic pancreatitis (CP) is a risk factor for osteoporotic fracture, but data on males with CP and fracture prevalence are sparse. We determined the association of sex and age using a large Veterans Administration database.

Methods: This was a retrospective analysis (1998–2007). Patients with CP (*International Classification of Diseases* code 577.1) and control subjects (without CP) were identified after exclusions and fracture prevalence (vertebral, hip, and wrist) were recorded.

Results: 453,912 Veterans Administration patients were identified (control subjects: 450,655 and patients with CP: 3257). Mean ages of control subjects and CP were 53.6 and 54.2 years ($P < 0.014$). Patients with CP had higher odds ratios of total fractures (2.35; 95% confidence interval [CI], 2.00–2.77), vertebral fracture 2.11 (95% CI, 1.44–3.01), hip fracture 3.49 (95% CI, 2.78–4.38), and wrist fracture 1.68 (95% CI, 1.29–2.18) when compared with control subjects. After adjusting for age group and etiology, patients with CP had increased odds of total fractures, vertebral fractures, and hip fractures ($P < 0.05$).

Conclusions: In this male-predominate Veterans Administration study, patients with CP were at increased risk of osteoporotic fractures. The risk was higher for hip fracture (>3 times) in patients with CP compared with control subjects. All patients with CP older than 45 years, irrespective of sex, should be screened for bone mineral density loss.

Key Words: chronic pancreatitis, fracture risk, metabolic bone disease, osteoporosis

Abbreviations: BMD - bone mineral density, CP - chronic pancreatitis, CI - confidence interval, FY - fiscal year, *ICD-9-CM - International Classification of Diseases, Ninth Revision, Clinical Modification*, VA - Veterans Administration

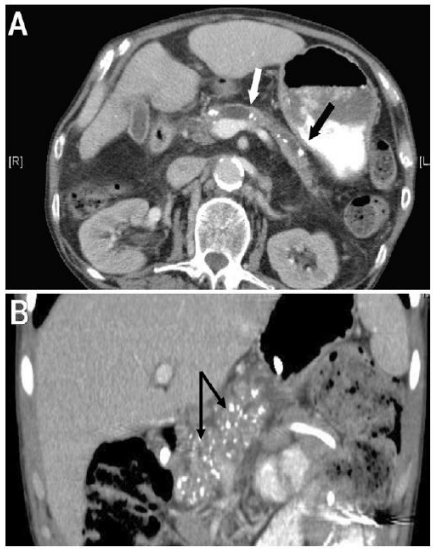
(*Pancreas* 2016;45: 355–361)

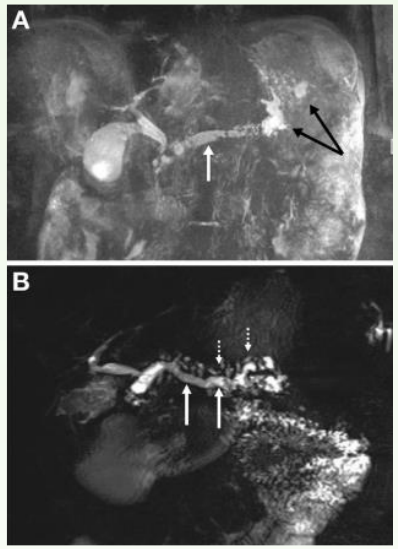
Clinical Review & Education

JAMA | Review

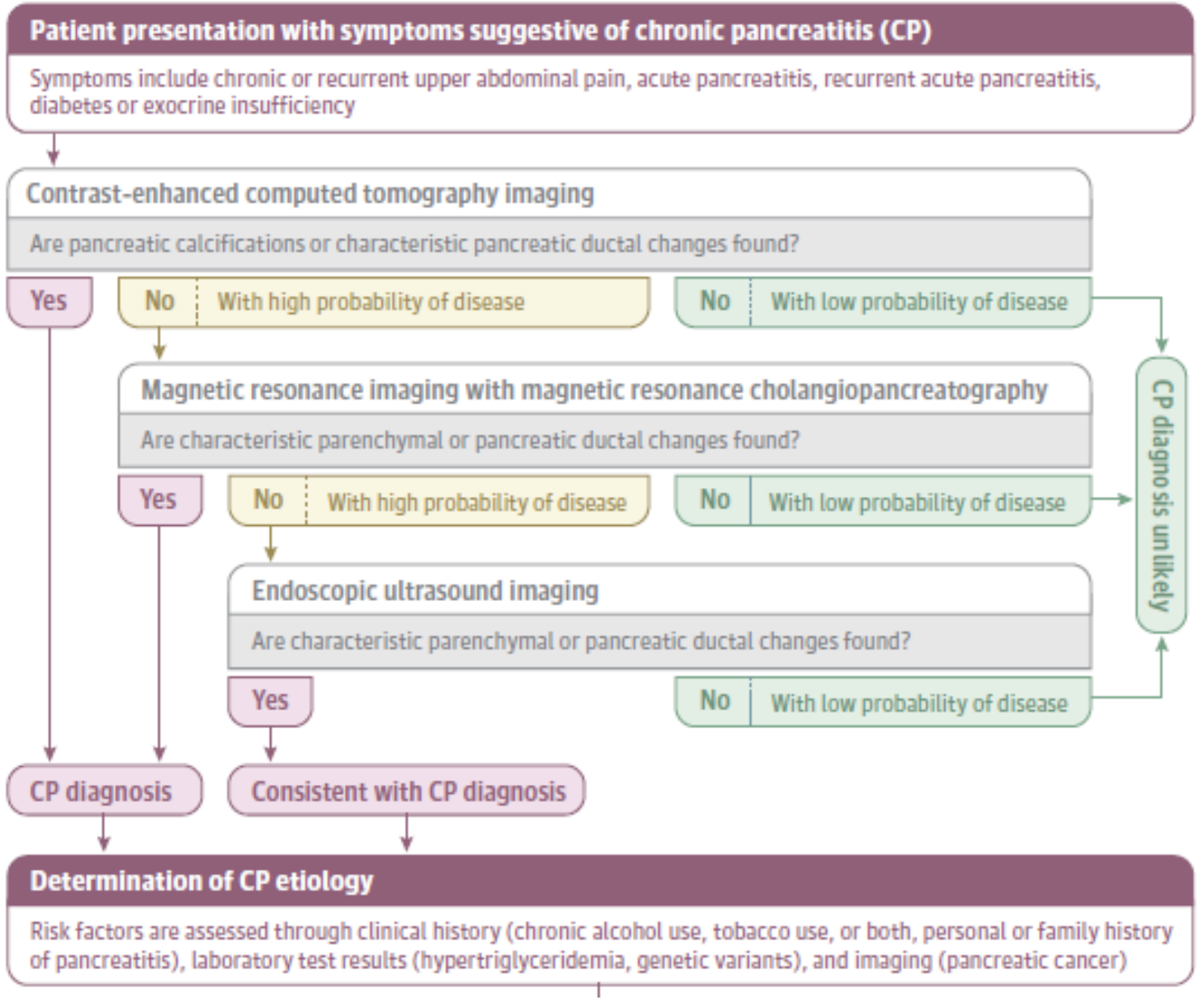
Diagnosis and Management of Chronic Pancreatitis
A Review

Vikesh K. Singh, MD, MSc; Dhiraj Yadav, MD, MPH; Pramod K. Garg, MD





Singh V, et al. JAMA 2019



Clinical Review & Education

JAMA | Review

Diagnosis and Management of Chronic Pancreatitis
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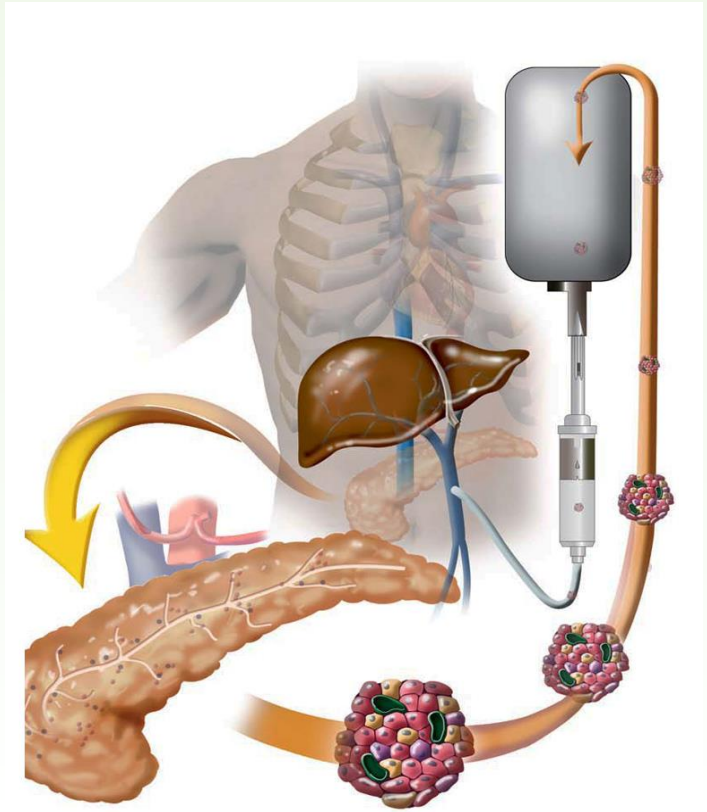
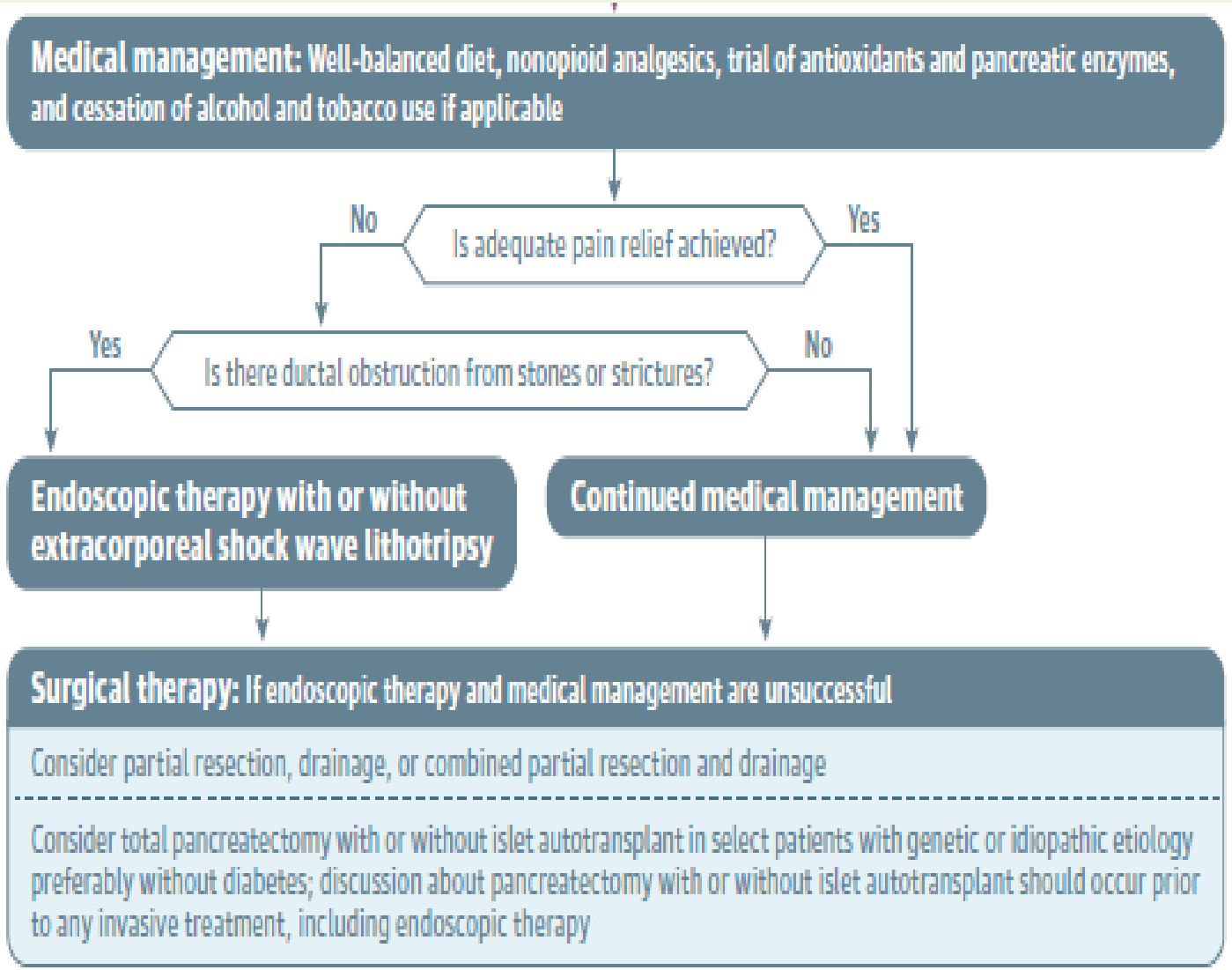




Total Pancreatectomy with Islet AutoTransplant (TPIAT)

Singh V, et al. JAMA 2019


"We must accept finite disappointment, but never lose infinite hope."
Rev. Dr. Martin Luther King, Jr.

There is HOPE !!

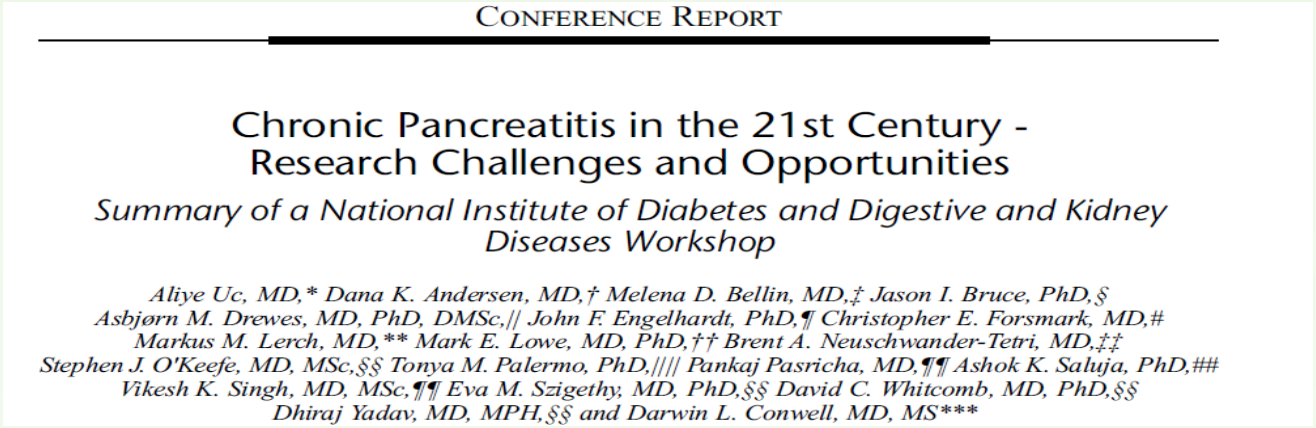
Chronic Pancreatitis: Managing a Difficult Disease

Phil A. Hart, MD[1] and Darwin L. Conwell, MD, MS[1]

Chronic pancreatitis is characterized by progressive, irreversible morphologic and functional changes that are most commonly attributed to environmental insults, particularly when there is a genetic or anatomic predisposition. Heavy alcohol use and cigarette smoking are the most common environmental risk factors, but both may be absent. Antecedent episodes of acute pancreatitis occur in about half of patients. Abdominal pain is the most common symptom and requires a tailored approach depending on the anatomic changes in the pancreas. Other clinical manifestations include diabetes mellitus, exocrine pancreatic insufficiency, metabolic bone disease, pancreatic cancer, and anatomic complications. Current disease management is centered on risk factor reduction and screening for and treating disease complications. There are no current therapies to delay or retard disease progression, but there are ongoing efforts to more fully understand the natural history of chronic pancreatitis and underlying mechanisms of disease. These studies are expected to provide insights that will transform our approach to disease management and provide increased hope to patients.

Am J Gastroenterol 2020;115:49–55. https://doi.org/10.14309/ajg.0000000000000421

REVIEW ARTICLE



CONFERENCE REPORT

Chronic Pancreatitis in the 21st Century - Research Challenges and Opportunities

Summary of a National Institute of Diabetes and Digestive and Kidney Diseases Workshop

Aliye Uc, MD, Dana K. Andersen, MD,† Melena D. Bellin, MD,‡ Jason I. Bruce, PhD,§ Asbjørn M. Drewes, MD, PhD, DMSc,// John F. Engelhardt, PhD,¶ Christopher E. Forsmark, MD,# Markus M. Lerch, MD,** Mark E. Lowe, MD, PhD,†† Brent A. Neuschwander-Tetri, MD,‡‡ Stephen J. O'Keefe, MD, MSc,§§ Tonya M. Palermo, PhD,//// Pankaj Pasricha, MD,¶¶ Ashok K. Saluja, PhD,## Vikesh K. Singh, MD, MSc,¶¶ Eva M. Szigethy, MD, PhD,§§ David C. Whitcomb, MD, PhD,§§ Dhiraj Yadav, MD, MPH,§§ and Darwin L. Conwell, MD, MS****

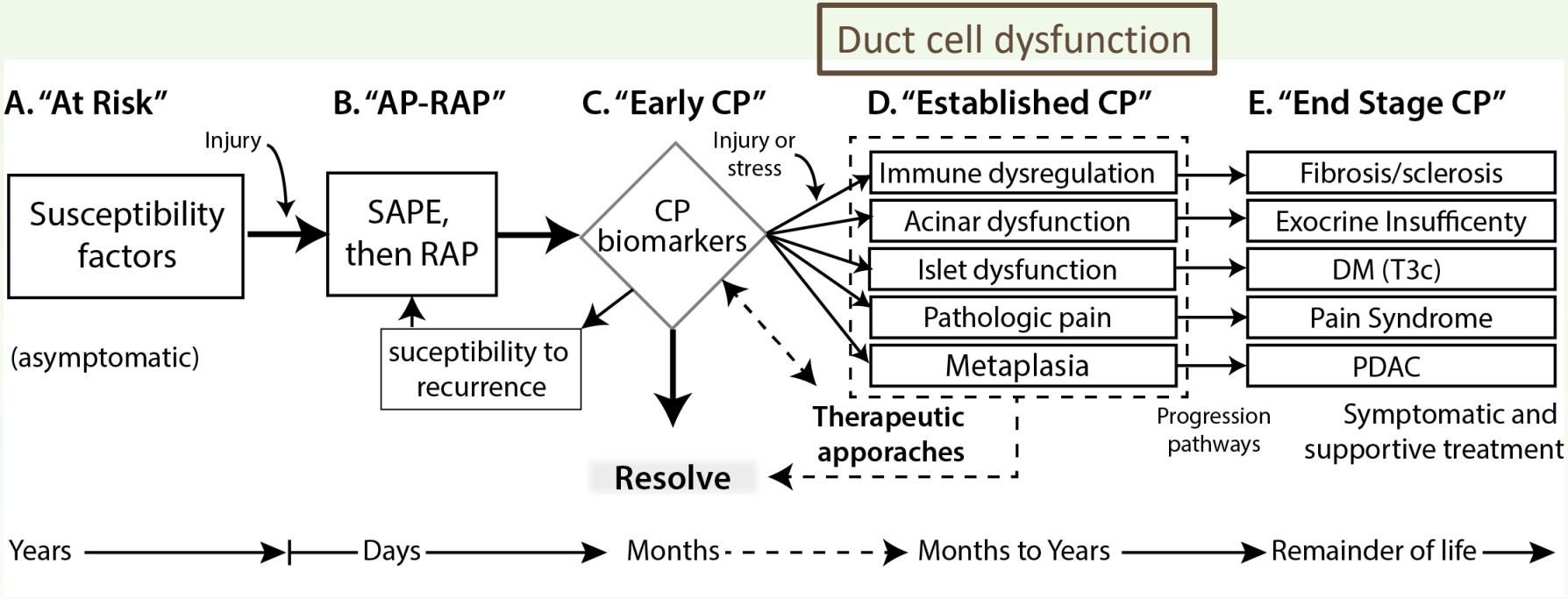
Research Gaps and Opportunities

- Improve and accurate assessment of maldigestion and EPI.
- Establish simpler, less invasive tools to measure acinar and ductal cell function from more easily obtained biological specimens such as urine or blood to screen for pancreatic disease.
- Develop RAP and CP biomarkers that can be used to better de- fine the stage, determine prognosis, assess severity, and stratify patients for medical or surgical intervention using the mechanistic definition framework.
- Provide evidence-based recommendations for proper dietary intake and the requirements for PERT (initiation, dose, timing, follow-up).
- Develop enzyme products requiring fewer pills and with better compliance and potency.

Research Gaps and Opportunities

- Develop long-term primary acinar and ductal epithelial cell culture models.
- Explore co-culture models (eg, acinar-duct, duct-islet, acinar- islet) to identify factors that regulate exocrine cell function and restitution.
- Define mechanisms by which gene mutations/variants cause pancreatic inflammation, ductal cell malfunction, and acinar cell loss.
- Design novel therapies that target restoring pancreatic acinar cells and/or manipulate ductal cells (ie, gene and cell-based therapies, CRISPR/Cas9, CFTR correctors and potentiators).
- Develop experiments to determine the critical age and time for intervention to reestablish appropriate stem cell niches for cell-based therapies in diseases that damage the exocrine pancreas.

The Black Box: Mechanistic Definition



Black Box Contents: Highly variable and protean signs, symptoms and imaging findings, various combinations of the following:

- Symptom(s): no symptoms, abdominal pain, nausea, maldigestion, glucose intolerance, IBS
- Pancreas Function: normal, cellular dysregulation (duct, acinar, islets)
- Pancreas Imaging: normal, EUS / MRI - minimal changes (Standard criteria, Cambridge 1-2)
- Histopathology: no usually available in clinical setting; FNB, fibrosis, atrophy, inflammation, lack of consensus pathologic definitions

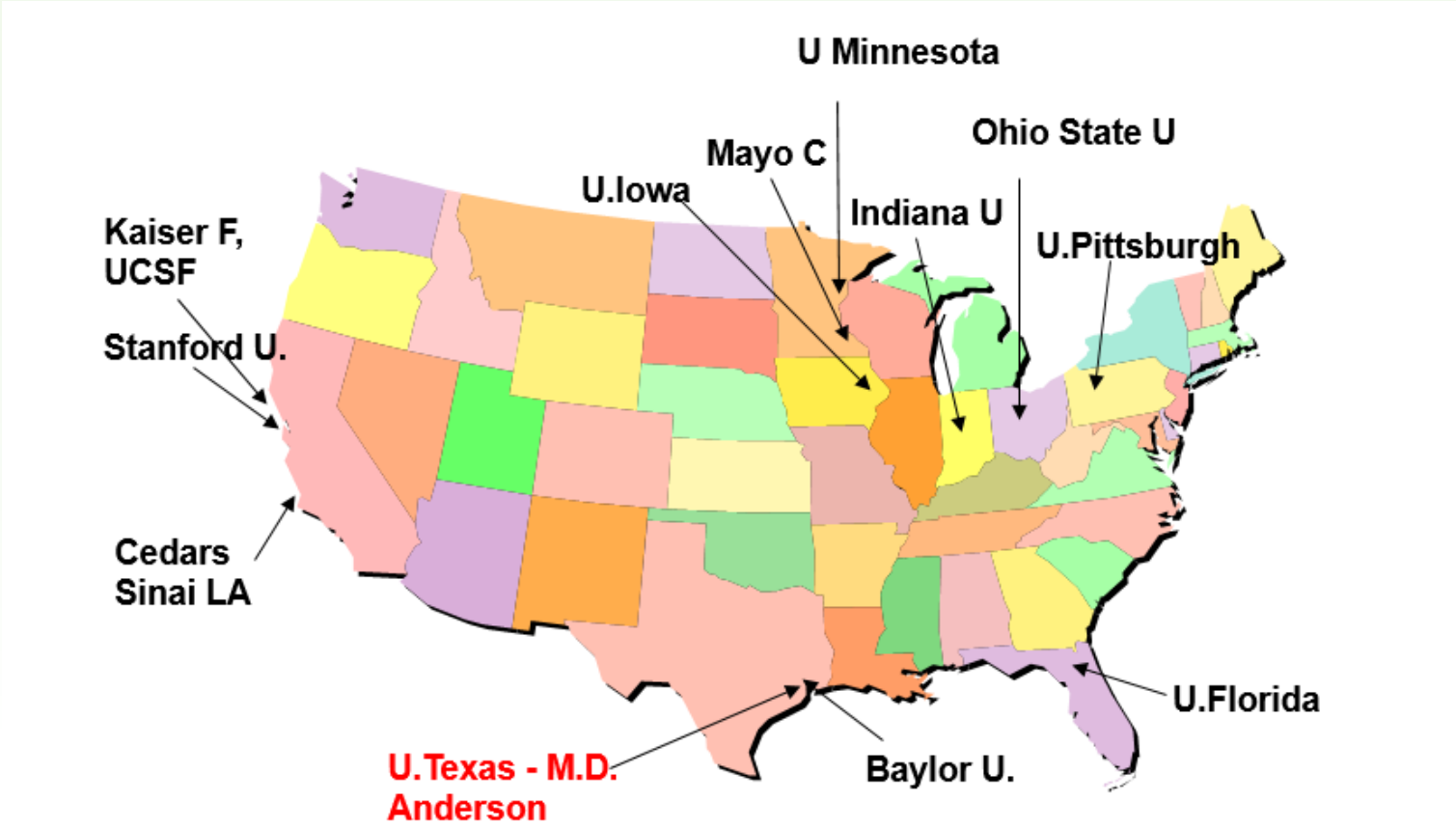
Research Opportunity:
DEFINITION yet to be determined

MORE LIKELY TO RETARD DISEASE SYMPTOMS AND PROGRESSION

Cross-Sectional: Biomarker Discover / Development

Longitudinal: Biomarker Validation / Clinical Implementation

NIH-NIDDK/NCI - Consortium for the Study of Chronic Pancreatitis Diabetes and Pancreatic Cancer



Established the Largest Prospective cohort of CP: PROCEED

CPDPC CONFERENCE REPORT

*PRO*spective Evaluation of Chronic Pancreatitis for *E*pid*E*miologic and Translational Stu*D*ies

Rationale and Study Design for PROCEED From the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer

Dhiraj Yadav, MD, MPH, Walter G. Park, MD,† Evan L. Fogel, MD, MSc,‡ Liang Li, PhD,§ Suresh T. Chari, MD,|| Ziding Feng, PhD,¶ William E. Fisher, MD,# Christopher E. Forsmark, MD,** Christie Y. Jeon, ScD,†† Aida Habtezion, MD, MSc,† Phil A. Hart, MD,‡‡ Steven J. Hughes, MD,§§ Mohamed O. Othman, MD,|||| Jo Ann S. Rinaudo, PhD,¶¶ Stephen J. Pandol, MD,## Temel Tirkes, MD,*** Jose Serrano, MD, PhD,††† Sudhir Srivastava, PhD, MPH,¶¶ Stephen K. Van Den Eeden, PhD,‡‡‡ David C. Whitcomb, MD, PhD,*§§§|||||| Mark Topazian, MD,|| and Darwin L. Conwell, MD, MSc,‡‡ on behalf of the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer (CPDPC)*

Yadav D, et al. Pancreas 2018.

PROCEED Study Objectives

PROCEED
PROspective Evaluation of Chronic Pancreatitis for Epidemiologic and Translational Studies

- Primary
  1. To establish **a model of longitudinal research cohort of adults with CP** and its complications
  2. To estimate the **risk of progression to suspected CP to definite CP,** development of new-onset diabetes and exocrine insufficiency in definite CP, and study how the risks are influenced by patient characteristics and conditions
  3. To test **predictive capability of candidate biomarkers** for diagnosis and prognosis of CP
  4. To develop a **framework for conducting biomarker, genetic and mechanistic studies** using clinical information and the biorepository developed as part of the longitudinal research cohort

- Secondary (several)

Established SOPs for collection of Biospecimens in CP cohort

CPDPC Conference Report

Standard Operating Procedures for Biospecimen Collection, Processing, and Storage

From the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer

William E. Fisher, MD, FACS, Zobeida Cruz-Monserrate, PhD,† Amy L. McElhany, MPH,* Gregory B. Lesinski, PhD,‡ Phil A. Hart, MD,† Ria Ghosh, MBA, MPH,§ George Van Buren, MD,* Douglas S. Fishman, MD,|| Jo Ann S. Rinaudo, PhD,¶ Jose Serrano, MD, PhD,# Sudhir Srivastava, PhD,¶ Thomas Mace, PhD,† Mark Topazian, MD,** Ziding Feng, PhD,§ Dhiraj Yadav, MD,†† Stephen J. Pandol, MD,‡‡ Steven J. Hughes, MD,§§ Robert Y. Liu, MS,|||| Emily Lu, MS,|||| Robert Orr, BS,¶¶ David C. Whitcomb, MD, PhD,** Amer S. Abouhamze, MHA,## Hanno Steen, PhD,*** Zachary M. Sellers, MD, PhD,††† David M. Troendle, MD,‡‡‡ Aliye Uc, MD,§§§ Mark E. Lowe, MD, PhD,|||||| and Darwin L. Conwell, MD,† on behalf of the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer (CPDPC)*

PROCEED

PROSPECTIVE EVALUATION OF CHRONIC PANCREATITIS FOR EPIDEMIOLOGIC AND TRANSLATIONAL STUDIES

Fisher W, et al. Pancreas 2018.

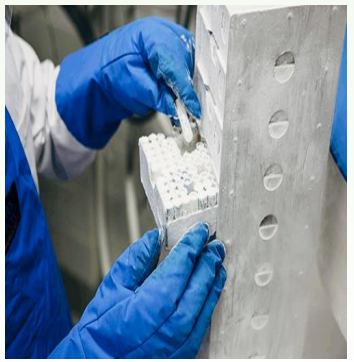
Established the PROCEED Biorepository which is ready for use (>100,000 aliquots already)

- According to the PRoBE design

Table 1: PROCEED Samples Collected and Shipped by Center*

Center	Samples Shipped (# of Shipments)	Samples Collected	% Shipped
Baylor	9,293 (13)	9,808	95
Cedars-Sinai	5,252 (9)	8,159	64
Indiana	9,328 (9)	17,701	53
Mayo	2,054 (3)	15,078	14
Stanford	7,202 (15)	11,062	65
OSU	8,390 (9)	12,381	68
UPMC	15,428 (14)	18,107	85
Florida	4,877 (8)	6,525	75
Kaiser	2,049 (5)	6,190	33
Total	63,873 (85)	105,011	61

*Stool samples are excluded from this table, as these continue to be shipped from centers to the Baylor College of Medicine Microbiome Center. Stool sample collection and shipping is presented in Table 2 below.



- Legacy samples outside of PROCEED also available for exploratory work

PROCEED
PROSPECTIVE EVALUATION OF CHRONIC PANCREATITIS FOR EPIDEMIOLOGIC AND TRANSLATIONAL STUDIES

PROCEED

PROSPECTIVE EVALUATION OF CHRONIC PANCREATITIS FOR EPIDEMIOLOGIC AND TRANSLATIONAL STUDIES

> 100,000 samples

Pepe, M., J Natl Cancer Inst, 2008
Cruz-Monserrate, Z., Pancreatology 2021

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

Biomarkers of Chronic Pancreatitis: A systematic literature review

Zobeida Cruz-Monserrate [a, b, *, 1], Kristyn Gumpper [a, b], Valentina Pita [a, b], Phil A. Hart [a], Christopher Forsmark [c], David C. Whitcomb [d], Dhiraj Yadav [d], Richard T. Waldron [e], Stephen Pandol [e], Hanno Steen [f, g], Vincent Anani [h], Natasha Kanwar [h], Santhi Swaroop Vege [h], Savi Appana [i], Liang Li [i], Jose Serrano [j], Jo Ann S. Rinaudo [k], Mark Topazian [h, 1], Darwin L. Conwell [a, 1], on behalf of the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer

[a] Department of Internal Medicine, Division of Gastroenterology, Hepatology, and Nutrition, The Ohio State University Wexner Medical Center, Columbus, OH, USA
[b] The James Comprehensive Cancer Center, The Ohio State University Wexner Medical Center, Columbus, OH, USA
[c] University of Florida, Gainesville, FL, USA
[d] University of Pittsburgh, Pittsburgh, PA, USA
[e] Cedars-Sinai Medical Center, Los Angeles, CA, USA
[f] Department of Pathology, Boston Children's Hospital, Boston, MA, USA
[g] Departments of Pathology, Boston Children's Hospital and Harvard Medical School, Boston, MA, USA
[h] The Mayo Clinic, Rochester, MN, USA
[i] The University of Texas MD Anderson Cancer Center, Houston, TX, USA
[j] Division of Digestive Diseases and Nutrition, National Institutes of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, USA
[k] Cancer Biomarkers Research Group, Division of Cancer Prevention, National Cancer Institute, Rockville, MD, USA

Prospective-specimen-collection, retrospective-blinded-evaluation (PRoBE) design

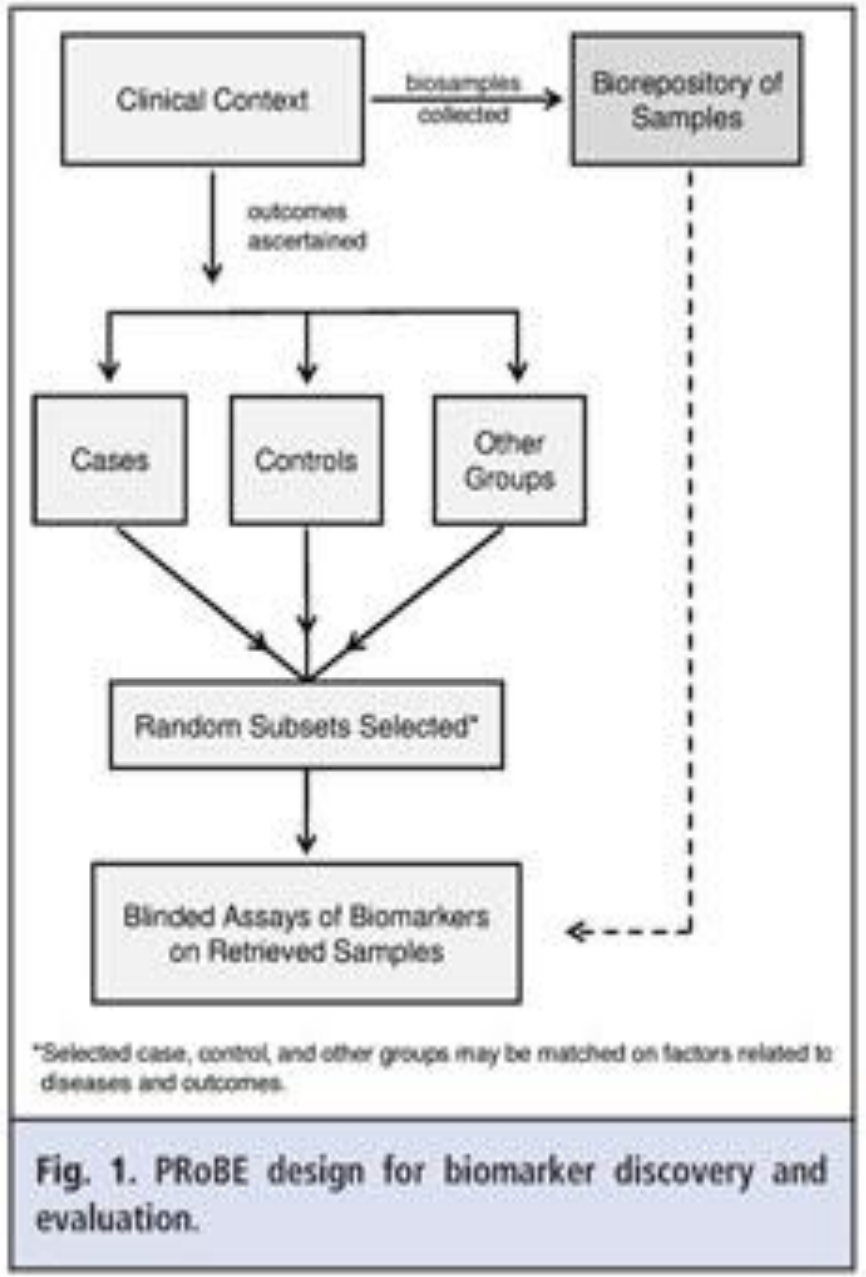


Fig. 1. PRoBE design for biomarker discovery and evaluation.

High Prevalence of Osteopathy in Chronic Pancreatitis: A Cross-sectional Analysis From the PROCEED Study

Phil A. Hart,[*] Dhiraj Yadav,[‡] Liang Li,[§] Savi Appana,[§] William Fisher,[‖] Evan Fogel,[¶] Chris E. Forsmark,[#] Walter G. Park,[**] Stephen Pandol,[‡‡] Mark D. Topazian,[§§] Stephen K. Van Den Eden,[‖‖] Santhi Swaroop Vege,[§§] David Bradley,[¶¶] Jose Serrano,[##] and Darwin L. Conwell,[*] on behalf of the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer (CPDPC)

*Division of Gastroenterology, Hepatology, and Nutrition, The Ohio State University Wexner Medical Center, Columbus, Ohio; ‡Division of Gastroenterology, Hepatology, and Nutrition, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; §Department of Biostatistics, MD Anderson Cancer Center, Houston, Texas; ‖Department of Surgery, Baylor College of Medicine, Houston, Texas; ¶Division of Gastroenterology and Hepatology, Indiana University, Indianapolis, Indiana; #Division of Gastroenterology, University of Florida, Gainesville, Florida; **Division of Gastroenterology & Hepatology, Stanford University, Stanford, California; ‡‡Division of Gastroenterology and Hepatology, Cedars-Sinai Medical Center, Los Angeles, California; §§Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota; ‖‖Division of Research, Kaiser Permanente Northern California, Oakland, California; ¶¶Division of Endocrinology, Diabetes, and Metabolism, The Ohio State University Wexner Medical Center, Columbus, Ohio; ##Division of Digestive Diseases and Nutrition, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland

BACKGROUND & AIMS: **Chronic pancreatitis (CP) is associated with osteopathy (osteoporosis or osteopenia). However, existing literature is mostly limited to retrospective or administrative studies that have not clearly defined the prevalence and risk factors. Our aim was to identify patient- and disease-related associations with osteopathy in a prospective cohort study of CP.**

METHODS: **We studied 282 subjects with definitive CP enrolled in the PROCEED study who had a baseline dual-energy X-ray absorptiometry (DXA) scan. Osteopenia and osteoporosis were defined using the lowest T-scores. Clinical data were collected using standardized case report forms. Comparisons were performed with a multivariate logistic regression model with forward selection to identify risk factors for osteopathy.**

RESULTS: **The majority of subjects had osteopathy on DXA scan (56.0%; 17.0% osteoporosis; 39.0% osteopenia). Subjects with osteopathy had a higher prevalence of traumatic (40.0% vs 26.4%; $P = .02$) and spontaneous fractures (3.9% vs 0; $P = .04$). On multivariate analysis, older age (odds ratio [OR], 1.29 per 5 years; 95% confidence interval [CI], 1.15–1.45), female sex (OR, 3.08; 95% CI, 1.75–5.43), white race (OR, 2.68; 95% CI, 1.20–6.01), and underweight body mass index category (OR, 7.40; 95% CI, 1.56–34.99) were associated with higher probability of osteopathy. There were no significant associations between osteopathy and patient and disease-related features of CP.**

CONCLUSION: **In the largest study of patients with CP who underwent DXA screening, the majority had osteopathy. There are overlapping risk factors with osteopathy in the general population, but the high prevalence in men and younger women supports the need for future investigations into the mechanisms of bone loss in CP.ClinicalTrials.gov number, NCT03099850.**

Keywords: Dual-energy X-ray absorptiometry; Fracture; Osteopenia; Osteoporosis.

The Ohio State University Division of Gastroenterology, Hepatology, and Nutrition: Section of Advanced Endoscopy and Section of Pancreatic Disorders

NATIONAL PANCREAS FOUNDATION CENTER

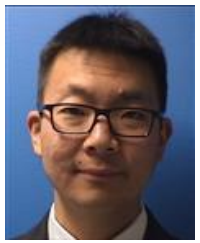
Nutrition and Metabolism of
Chronic Pancreatitis
Dr. Hart
(Director Pancreatic Disorders)
(U01,U01 DK LRP)

Obesity and Pancreas
Cancer
(Director Molecular and Cell Biology)
Dr. Cruz-Monserrate
(R01, R21,NPF, Orien, Pelotonia)

National Cancer Institute
Early Detection Research Network
DCP

Pancreas Cancer and
Pancreatitis
Immunology
Dr. Mace (KL2)

Dr. Jalil



Dr. Han
Dr. Han (R21, DK LRP)

Acute Pancreatitis and
Advanced Endoscopy
(Director Advanced Endoscopy)
Dr. Papachristou (U01, U01, DoD)

Diagnosis
and ablation of Pancreas Cysts
Confocal Laser Endomicroscopy
Dr. Krishna (R01, ACG, NPF, Orien)

Dr. Lee

Chronic Pancreatitis:
Diagnosis and
Treatment
Dr. Conwell (U01, U01 R21)

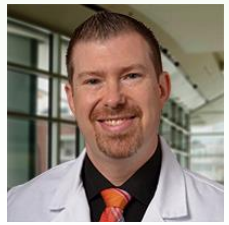
PROCEED
PROSPECTIVE EVALUATION OF CHRONIC PANCREATITIS FOR EPIDEMIOLOGIC AND TRANSLATIONAL STUDIES

Autologous Islet
Transplantation
in Chronic Pancreatitis
Dr. Lara (R01)

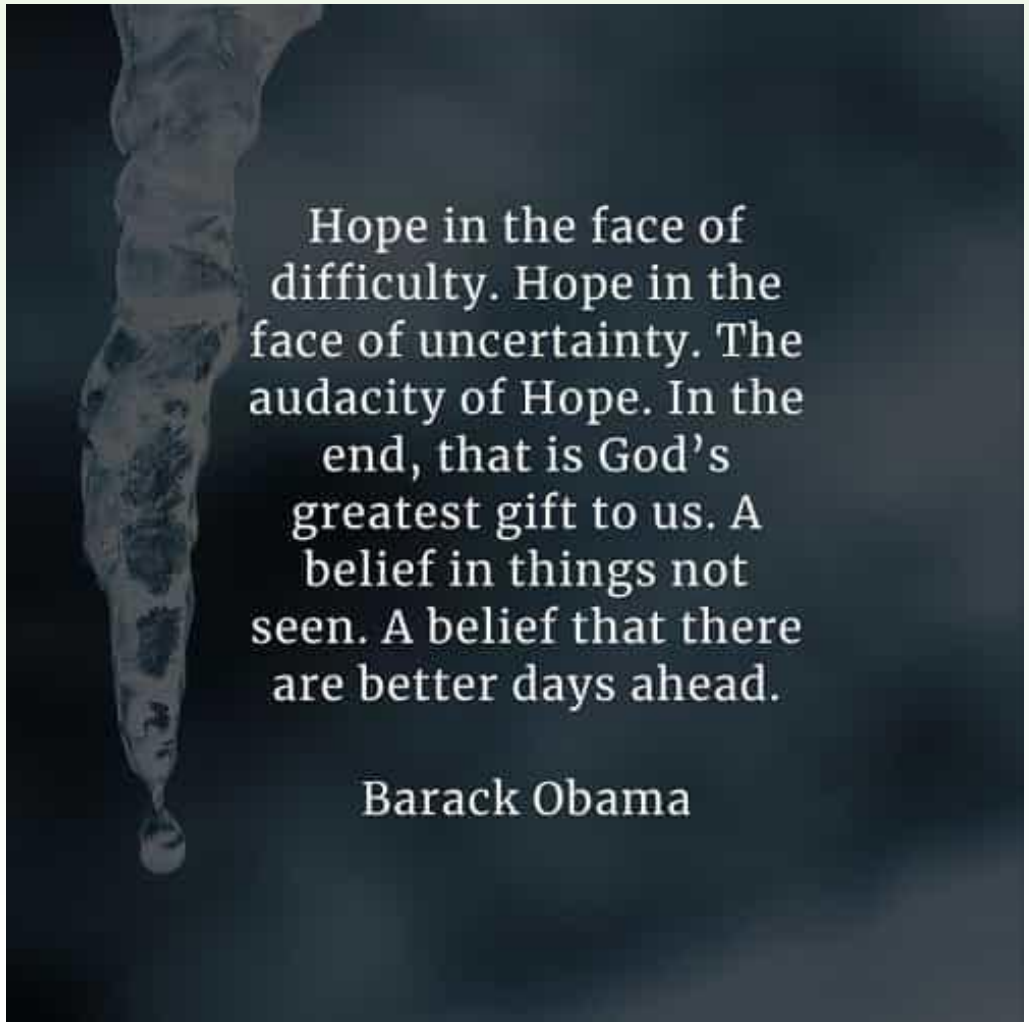
POST
Advancing Treatment for Pancreatitis: A Prospective Observational Study of TPIAT (POST)

Endoscopic Sphincterotomy
in Acute Recurrent Pancreatitis
Dr. Groce (U01)

HARP



There is Always Hope



CME/MOC QUESTION

Which of the following are long term outcomes of chronic pancreatitis?

Choose the BEST answer:

1. Endocrine Dysfunction (Diabetes)
2. Osteopathy (Hip fracture)
3. Cancer
4. Exocrine Dysfunction (Steatorrhea)

A. 1,2 and 3 are true
B. 1 and 3 are correct
C. 2 and 4 are true
D. All of the above are correct

CME/MOC ANSWER

Answer: D.

All of the above [Endocrine Dysfunction (Diabetes), Osteopathy (Hip fracture), Cancer, and Exocrine Dysfunction (Steatorrhea)] are outcomes observed in patients with chronic pancreatitis

Reference: Gardner, T et al Am J Gastroenterol

- Clinical Practice Guidelines: Chronic Pancreatitis

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