American Pancreatic Association Practice Guidelines in Chronic Pancreatitis

Evidence-Based Report on Diagnostic Guidelines

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Abstract: The diagnosis of chronic pancreatitis remains challenging in early stages of the disease. This report defines the diagnostic criteria useful in the assessment of patients with suspected and established chronic pancreatitis. All current diagnostic procedures are reviewed, and evidence-based statements are provided about their utility and limitations. Diagnostic criteria for chronic pancreatitis are classified as definitive, probable, or insufficient evidence. A diagnostic (STEP-wise; survey, tomography, endoscopy, and pancreas function testing) algorithm is proposed that proceeds from a noninvasive to a more invasive approach. This algorithm maximizes specificity (low false-positive rate) in subjects with chronic abdominal pain and equivocal imaging changes. Furthermore, a nomenclature is suggested to further characterize patients with established chronic pancreatitis based on TIGAR-O (toxic, idiopathic, genetic, autoimmune, recurrent, and obstructive) etiology, gland morphology (Cambridge criteria), and physiologic state (exocrine, endocrine function) for uniformity across future multicenter research collaborations. This guideline will serve as a baseline manuscript that will be modified as new evidence becomes available and our knowledge of chronic pancreatitis improves.

Key Words: chronic pancreatitis, diagnosis, guidelines, evidence-based

At the 2011 meeting of the American Pancreatic Association (APA), a chronic pancreatitis (CP) conference was held to review the medical literature to develop the first US practice guideline for CP. The APA Practice Guidelines in Chronic Pancreatitis is a 3-part evidence-based document that reviews the current literature on the diagnosis (part 1), treatment (part 2), and management of complications (part 3) of CP. The objective of this report was to provide an initial platform on which to build further evidence-based recommendations for the management of CP as new evidence becomes available.

Chronic pancreatitis is characterized by chronic progressive pancreatic inflammation and scarring, irreversibly damaging the pancreas and resulting in loss of exocrine and endocrine function. It was first described in the medical literature in 1788 by Sir Thomas Cawley; however, a review in the New England Journal of Medicine stated that despite the “thousands of reports dealing with this disease, it remains an enigmatic process containing illness.” Fortunately, since that landmark publication, there have been major advances in our understanding of CP pathogenesis and pathophysiology, including pancreatic fibrosis, etiologic risk factors, natural history, and associated genetic and epigenetic changes. Clinical diagnostic tools have also seen considerable improvement with advances in endoscopic and radiologic imaging techniques, and the development of endoscopy-assisted pancreas function testing has widened its clinical use.

The clinical manifestations of CP can include abdominal pain, steatorrhea, and diabetes, as well as numerous acute and chronic complications. Current treatments can only provide temporary pain relief and manage complications but are unable to arrest or slow the progression of this often debilitating illness. In addition, a subset of CP patients develops pancreatic adenocarcinoma, which is generally advanced at the time of diagnosis due to the marked morphologic changes in the gland that can “mask” tumors, preventing early detection.

Both basic scientists and clinical researchers are actively investigating the pathogenesis of CP. The resulting advances will certainly improve diagnosis, management, and treatment of CP in the future, but until then, evidence-based current practice strategies are needed. Where there is no clear evidence, expert opinion from experienced basic scientists, gastroenterologists, therapeutic endoscopists, and surgeons, who specialize in pancreatology, must prevail. Unlike acute pancreatitis (AP), there is a paucity of practice guidelines for CP in the medical literature. Italian, German, and Spanish Consensus Guidelines for Chronic Pancreatitis have recently been published, and
both provide valuable insight into the numerous challenges facing diagnosis and management of this complex disorder.

**MATERIALS AND METHODS**

The primary aim of this report was to provide current practice guidelines for CP from an evidence-based review of the medical literature and expert opinion. The development of the APA Practice Guidelines in Chronic Pancreatitis involved the following steps:

1. A 1-day multidisciplinary symposium, led by leaders in the field of CP, to review the literature on CP as it pertains to diagnosis, treatment, and management of complications. The organization committee (D.L.C., S.S.V., and C.E.F.) invited participation from speakers, moderators, and thought leaders specializing in gastroenterology, surgery, and therapeutic endoscopy from numerous academic centers throughout the United States.
2. The final program was approved by the APA and organized into 3 sessions as follows: (1) diagnostic guidelines, (2) treatment guidelines, and (3) complications and long-term management.
3. Experts reviewed the medical literature and presented evidence pertaining to CP, epidemiology, diagnosis, treatment, and management of its complications.
4. Each of the 3 sessions concluded with commentary from thought leaders summarizing the major challenges facing physicians treating patients with CP.
5. Open discussions and breakout meetings were organized after each session to allow for all 2011 APA conference attendees to participate in debate and discussion of controversial areas and to assist in the development of future practice guidelines.
6. The conference lectures were transcribed and edited by the speakers, then reviewed and collated by session chairpersons and moderators into a working draft for each of the 3 sessions.
7. For recommendations, APA used the classification by the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) with slight changes. The Strength of recommendation is either strong or conditional (weak). Factors influencing strong recommendation include the quality of evidence, presumed patient-important outcomes, and cost. Conditional recommendation denotes the variability in preferences and values or more uncertainty, implying less certainty, higher cost, or resource consumption. Quality of evidence is high (A, further research unlikely to change confidence in the estimate of the clinical effect), moderate (B, further research may change confidence), low (C, further research very likely to impact confidence), and very low (D, an estimate of the effect is uncertain). However, in the GRADE approach, high-quality evidence may not translate into strong recommendation, and weak evidence may result in a strong recommendation.26
8. The conference organization committee reviewed and edited the session drafts, compiling a working draft of the APA Chronic Pancreatitis Practice Guidelines.
9. The working draft was submitted to independent reviewers, experts in each major session area, for critique and commentary.
10. A final draft was submitted to the APA Governing Board for editorial review.
11. After further editorial revisions, the official APA Practice Guideline for Chronic Pancreatitis was finalized and submitted for peer-reviewed publication.

**EVIDENCE-BASED REPORT ON DIAGNOSTIC GUIDELINES**

Chronic pancreatitis should be in the differential diagnosis of a patient with typical features of epigastric pain with radiation to the back, steatorrhea, weight loss, or recurrent AP. Patients generally have known risk factors for CP such as moderate to heavy alcohol or tobacco exposure. Because the disease is irreversible and carries a social stigma, the diagnosis needs to be certain (ie, definitive, probable) before labeling a patient with this chronic illness. Furthermore, clinical evaluation is warranted in patients with a high suspicion of disease to rule out pancreas carcinoma that can mimic both its clinical and imaging presentation.

In general, the radiologic and endoscopic evaluation of a patient with suspected CP should progress from a least invasive to more invasive approach to establish a diagnosis. A computed tomography (CT) scan of the pancreas is usually the initial imaging modality of choice. Patients with equivocal or mild CT imaging findings or refractory symptoms may be referred to specialized centers for additional studies such as magnetic resonance imaging (MRI)/secretin-enhanced magnetic resonance cholangiopancreatography (MRCP) or endoscopic procedures such as endoscopic ultrasound (EUS), endoscopic retrograde cholangiopancreatography (ERCP), and pancreas function testing.

The posttest probability of chronic pancreatic disease is markedly influenced by the clinical history, physical examination, etiologic risk factor profile, and results of radiologic and endoscopic imaging tests. Despite exhaustive attempts at diagnosis, up to 5% to 10% of patients cannot be clearly diagnosed with certainty because of disagreement or discordance between imaging and endoscopic findings.

This article is the first of a 3-part guideline proposed by the APA to assist physicians caring for individuals with suspected CP. We review the current epidemiology, pathology, radiology, endoscopy, and physiologic testing methods and procedures that are currently utilized in the evaluation of suspected CP. We present evidence to support a definitive diagnosis and propose a nomenclature that can be used at academic centers to standardize clinical research reporting of data.

It is our hope that this initial document will serve as an initial platform on which to build further evidence-based recommendations as more knowledge becomes available and as our understanding of CP pathophysiology improves.

**Topic 1. Epidemiology and Risk Factors**

- Dhiraj Yadav, MD, University of Pittsburgh Medical Center, Pittsburgh, PA (lead discussant)

**Evidence-Based Medicine Statements**

1. Data on population-based estimates of CP are emerging.
2. A small fraction of patients progress from AP to CP.
3. Alcohol and smoking are independent risk factors for CP. Both are associated with disease progression, and their risks are likely multiplicative.
4. The spectrum of risk factors for CP has broadened.
5. Genetic discoveries are rapidly uncovering new susceptibility factors. Knowledge of gene and gene-environment interactions may translate into new diagnostic and treatment paradigms.

**Level of Evidence**

1. Conditional recommendation (level of evidence, low)
2. Conditional recommendation (level of evidence, moderate)
3. Strong recommendation (level of evidence, high)
In the past 50 years, we have learned a lot about the epidemiology and risk factors associated with CP. Most epidemiologic data for CP come from large case series and cross-sectional studies. Population-based data on CP are scarce due to its low incidence and prevalence, difficulty in establishing an early diagnosis, and variable time course for progression from AP to CP. The overall incidence of CP (Table 1) ranges from 4.4 to 11.9 per 100,000 per year.27–34 The incidence is higher in men than in women by a factor of 1.5 to 3. Data on prevalence of CP are even scarcer and range from 36.9 to 41.8 per 100,000 persons.29,30

The etiology of CP has traditionally been classified as alcohol, hereditary, obstructive, hyperlipidemia, and idiopathic (Table 2). The TIGAR-O risk factor classification has been proposed10 as follows: toxic-metabolic, idiopathic, genetic, autoimmune, recurrent and severe AP-associated CP, and obstructive etiologic factors. This classification system was developed with the premise that the risk of developing CP in an individual is determined by the presence of 1 or more risk factors. A similar MANNHEIM classification has been proposed that also recognizes the role of multiple etiologic factors in disease development.35

Alcohol and smoking contribute greatly to the development of CP. Alcohol is the single most common etiologic factor and

### TABLE 1. Incidence and Prevalence of CP in Population-Based Studies27–34

<table>
<thead>
<tr>
<th>Design</th>
<th>Population</th>
<th>Year(s)</th>
<th>Incidence (per 100,000)</th>
<th>All</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chart review</td>
<td>Luneberg County, Germany</td>
<td>1988–1995</td>
<td>6.4</td>
<td>8.2</td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moravia, Czech Republic</td>
<td>1999</td>
<td>7.9</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Olmsted County, Minnesota</td>
<td>1997–2006</td>
<td>4.4</td>
<td>5.2</td>
<td>3.8</td>
<td></td>
</tr>
<tr>
<td>Survey</td>
<td>Japan</td>
<td>2007</td>
<td>11.9</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Administrative data</td>
<td>Britain</td>
<td>1999–2000</td>
<td>8.6</td>
<td>12.4</td>
<td>4.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>United States</td>
<td>1988–2004</td>
<td>8.1</td>
<td>4.1</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>The Netherlands</td>
<td>2004</td>
<td>8.4</td>
<td>11.4</td>
<td>5.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Allegheny County, Pennsylvania</td>
<td>1996–2005</td>
<td>7.8</td>
<td>8.3</td>
<td>7.2</td>
<td></td>
</tr>
<tr>
<td>Prevalence</td>
<td>Survey</td>
<td>Japan</td>
<td>36.9</td>
<td>53.2</td>
<td>21.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chart review</td>
<td>Olmsted County, Minnesota</td>
<td>2006</td>
<td>41.8</td>
<td>51.5</td>
<td>33.9</td>
</tr>
<tr>
<td></td>
<td>NA, not available.</td>
<td></td>
<td></td>
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</tbody>
</table>

### TABLE 2. Classification System for Etiology and Risk Factors for CP10,35

<table>
<thead>
<tr>
<th>Classification for CP Etiology</th>
<th>Traditional</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alcohol, idiopathic, hereditary, obstructive, hyperlipidemia</td>
</tr>
<tr>
<td><strong>TIGAR-O</strong></td>
<td></td>
</tr>
<tr>
<td>Toxic-metabolic: alcohol, tobacco smoking, hypercalcemia, hyperlipidemia, chronic renal failure, medications, toxins</td>
<td></td>
</tr>
<tr>
<td>Idiopathic: early onset, late onset, tropical</td>
<td></td>
</tr>
<tr>
<td>Genetic mutations: PRSS1, CFTR, SPINK1, others</td>
<td></td>
</tr>
<tr>
<td>Autoimmune: isolated, syndromic</td>
<td></td>
</tr>
<tr>
<td>Recurrent and severe AP-associated CP: postnecrotic (severe AP), vascular disease/ischemic, postirradiation</td>
<td></td>
</tr>
<tr>
<td>Obstructive: pancreas divisum, sphincter of Oddi disorders, duct obstruction (eg, tumor), posttraumatic pancreatic duct scars</td>
<td></td>
</tr>
<tr>
<td><strong>MANNHEIM</strong></td>
<td></td>
</tr>
<tr>
<td>M indicates multiple risk factors including:</td>
<td></td>
</tr>
<tr>
<td>Alcohol consumption: excessive (&gt;80 g/d), increased (20–80 g/d), moderate (&lt;20 g/d)</td>
<td></td>
</tr>
<tr>
<td>Nicotine consumption</td>
<td></td>
</tr>
<tr>
<td>Nutritional factors: high calorie proportion of fat and protein, hyperlipidemia</td>
<td></td>
</tr>
<tr>
<td>Hereditary factors: hereditary, familial, idiopathic (early onset, late onset), tropical</td>
<td></td>
</tr>
<tr>
<td>Efferent duct factors: pancreas divisum, annular pancreas and other congenital abnormalities of the pancreas, pancreatic duct obstruction (eg, tumors), posttraumatic pancreatic duct scars, sphincter of Oddi dysfunction</td>
<td></td>
</tr>
<tr>
<td>Immunological factors: autoimmune pancreatitis</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous and rare metabolic disorders: hypercalcemia, hyperparathyroidism, chronic renal failure, drugs, toxins</td>
<td></td>
</tr>
</tbody>
</table>
accounts for 44% to 65% cases in population- and nonpopulation-based studies.\textsuperscript{6,46–49} Compared with the general population, the spectrum of alcohol consumption in patients with CP is clearly shifted to the right. The prevalence of pancreatitis in the setting of alcoholism is 3 to 6 times higher when compared with nondrinkers.\textsuperscript{47} and the absolute risk of pancreatitis among heavy drinkers is 2.5% to 3%.\textsuperscript{47,48} There seems to be a threshold of 4 to 5 drinks/d of alcohol consumption that clearly increases the risk of developing CP.\textsuperscript{12,48} Even at lower levels of consumption, alcohol likely plays a disease-modifying role. Experimental data generated using hyperstimulation models have demonstrated that heavy alcohol exposure increases the susceptibility of the pancreas to other injury\textsuperscript{49–51}; and after the initiation of pancreatic injury, alcohol modifies the immune response.\textsuperscript{52}

The association between smoking and CP is more uniform across epidemiologic studies. Smoking is a dose-dependent cofactor for causation of CP.\textsuperscript{12,53–55} The risk of developing CP in subjects smoking less than 1 pack of cigarettes per day is 2.4 (0.9–6.6) and increases to 3.3 (1.4–7.9) in those smoking more than 1 pack per day. Overall, smokers are on average 3 times more likely to develop CP compared with nonsmokers (pooled risk estimate, 2.8 [1.7–4.8]). More importantly, smoking cessation reduces the risk ratio estimate for CP by about 50% from 2.4 (1.8–4.2) in current smokers to 1.4 (1.1–1.9) in former smokers.\textsuperscript{60} Similarly, early smoking cessation after clinical onset of CP has been shown to reduce the risk of developing calcifications, whereas continued smoking is associated with increased risk of disease progression.\textsuperscript{61} The risk associated with smoking and alcohol together is important and likely multiplicative.\textsuperscript{62} Although alcohol and smoking increase the risk of progression individually, disease progression is more likely in the setting of continued alcohol and smoking.\textsuperscript{62}

Several genetic variations have been associated with pancreatitis including \textit{PRSS1}, \textit{PRSS2}, \textit{SPINK1}, \textit{CTRC}, \textit{CASR}, and \textit{CFTR}.\textsuperscript{65–75} The role of these gene mutations in CP is becoming increasingly recognized and better understood. It is important to note that these genetic mutations are all primarily linked to the trypsin pathway; the proportion of CP with known genetic mutations is small, and the association of these genetic variations is much stronger in the nonalcoholic etiologies compared with alcoholic pancreatitis (Table 3). Furthermore, specific mutations have been associated with varying degrees of genetic penetrance (80% for \textit{PRSS1}), and varying risk of idiopathic pancreatitis (\textit{CFTR}), tropical pancreatitis (\textit{CTRC}), and nonalcoholic CP (\textit{SPINK1}).

The pathogenesis of CP can likely be summarized by a 2-hit hypothesis model. In the setting of preexisting AP risk factors (genetic, metabolic, environmental), an initial first AP hit initiates or activates the immune system, followed by post-AP, followed by complete recovery or progression to CP.\textsuperscript{64}

In summary, population-based data on the epidemiology of CP are emerging and improving our understanding of the epidemiology, risk factors, and pathogenesis of the disease. The spectrum of risk factors for CP has broadened. Alcohol and smoking are independent risk factors for CP and interact in a multiplicative manner. Continuous alcohol and smoking abuse are associated with disease progression. Calculating attributable risk for individual risk factors

<table>
<thead>
<tr>
<th>Gene</th>
<th>Gene Name</th>
<th>Consequence</th>
<th>Prevalence, %</th>
<th>General Population</th>
<th>CP</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRS1</td>
<td>Cationic trypsinogen</td>
<td>Increased trypsinogen activation, decreased trypsin degradation</td>
<td>&lt;0.01</td>
<td>2–3</td>
<td>Penetrance for AP (80%), CP (40%)</td>
<td></td>
</tr>
<tr>
<td>SPINK1</td>
<td>Pancreatic secretory trypsin inhibitor</td>
<td>Failure of trypsin degradation</td>
<td>3–8</td>
<td>8</td>
<td>*Acute phase protein</td>
<td></td>
</tr>
<tr>
<td>CTRC</td>
<td>Chymotrypsin C</td>
<td>Failure of trypsin degradation</td>
<td>≤1</td>
<td>3–4</td>
<td>Risk higher in tropical/idiopathic CP</td>
<td></td>
</tr>
<tr>
<td>CASR</td>
<td>Calcium sensing receptor</td>
<td>Increased extracellular ionized calcium; increased trypsin activation and failed trypsin degradation</td>
<td>10</td>
<td>18</td>
<td>May have role in alcohol-related pancreatitis or hyperparathyroidism-induced pancreatitis</td>
<td></td>
</tr>
<tr>
<td>CFTR</td>
<td>Cystic fibrosis transmembrane conductance receptor</td>
<td>Impaired flushing of pancreatic ducts leading to trypsin activation</td>
<td>2–3 (AF508)</td>
<td>6</td>
<td>*Risk in pancreas sufficient patients: ~25%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5 (other)</td>
<td>8–9</td>
<td>*About one third of idiopathic CP are compound heterozygotes</td>
<td></td>
</tr>
</tbody>
</table>

*Increased recognition of the role of atypical/benign mutations (eg, R75Q)

FIGURE 1. Pancreas with CP. The stomach is at the top, the duodenum at the lower left, and the spleen on the right with the pancreas extending from the spleen to the duodenum. The pancreas is small, probably because of atrophy. The massively dilated main duct with a white stone is seen in the head and body of the pancreas. These are all characteristics of CP. Photo courtesy of Edward Bradley.
is difficult due to the complex nature of the disease and the variability of genetic and epigenetic factors. However, it is likely that the attributable risk of alcohol for CP is approximately 40% and that of smoking approaches 25%. Only a small fraction of patients with AP progress to CP. Genetic discoveries are rapidly unraveling new susceptibility factors, and the knowledge of gene and gene-environment interactions will likely translate into targeted diagnostic and treatment strategies.

**Anatomic Pathology-Based Statements**

1. Chronic pancreatitis is characterized by atrophy and fibrosis of the exocrine tissue with or without chronic inflammation.
2. Scarring of the parenchyma may be focal, patchy, or diffuse.
3. Progressive fibrosis and atrophy may lead to exocrine insufficiency (steatorrhea) followed by endocrine insufficiency (diabetes).
4. Autoimmune pancreatitis can mimic pancreas carcinoma.

**Level of Evidence**

The usual level of evidence statements are generally not used in anatomic pathology.

The pathology of CP varies with etiology, but there are changes that are present in all types. Typical changes seen at the gross level include reduction in size of the pancreas, dilatation of ducts, loss of lobular pattern in areas of scarring, and the presence of stones in the ducts (Fig. 1). Several of these features are variable and may not be seen in all cases.

Histologically, the 2 most common features of CP are loss of acinar tissue (atrophy) and fibrosis. The fibrosis may surround the lobules (perilobular or interlobular fibrosis) or extend into the lobules of acinar tissue (intralobular fibrosis) (Figs. 2, 3). A chronic inflammatory infiltrate may be present (Fig. 2), but this feature is highly variable and disappears late in the course of CP (Fig. 3). A diagnosis of CP may be made on the basis of atrophy and fibrosis in the absence of other changes. Islets often survive until late in the course of the disease—becoming more closely spaced as acinar tissue is lost (Fig. 4). In cystic fibrosis, which may be regarded as a special form of CP, there is dilatation of ducts resulting from the abnormal secretions with progressive fibrosis and loss of acinar tissue (Fig. 5).

Chronic pancreatitis can be a patchy or localized process with regional involvement (Fig. 6). This is best understood by...
considering the mechanisms of pathogenesis, in particular the necrosis-fibrosis hypothesis, which posits that CP develops as a result of multiple episodes of AP with necrosis and scarring. This process may be patchy at first, progressing to a diffuse pattern after multiple episodes. This is commonly considered to be the mechanism in alcoholic CP, paraduodenal CP, and likely hereditary pancreatitis. On the other hand, duct obstruction can lead to progressive fibrosis and loss of acinar tissue that may be localized or segmental, as in the presence of an obstructing neoplasm, or may be diffuse as is characteristic of cystic fibrosis.

In a review focused on alcoholic pancreatitis, we find the statement that “both alcoholic and nonalcoholic CP result in indistinguishable pancreatic damage.” A recently reported international comparison study provides evidence that the participating pathologists did not distinguish between alcoholic and obstructive CP; although they did become proficient at recognizing autoimmune pancreatitis (AIP) and its subtypes. Autoimmune pancreatitis is probably the most histologically distinct type of CP (Fig. 7). However, some expert pathologists do observe characteristics that distinguish different CP etiologies, thereby providing a basis for subclassification. Klöppel provides a histologic classification that includes alcoholic, hereditary, autoimmune, paraduodenal, and obstructive CP based on differences in the prevalence of various criteria such as necrosis, pseudocyst, fibrosis, duct lumen, duct contents, and duct epithelium. For example, necrosis and pseudocyst are much more likely to be seen in alcoholic CP than in the other forms. However, there is clearly an overlap of most histologic features among all types. A universal histologic grading and scoring system is needed to correlate clinical features with surgical pathologic findings.

In summary, atrophy and fibrosis of the exocrine tissue are the key features seen in CP. There may or may not be evidence of chronic inflammation, but it is quite appropriate to refer to CP as a fibroinflammatory disease. The scarring can be focal initially and may progress to become diffuse. The loss of acinar tissue may result in exocrine insufficiency and ultimately loss of islet tissue with diabetes. Acute phase pseudocysts may persist in CP that has developed via the necrosis-fibrosis pathway.

**Topic 3. Chronic Pancreatitis: Ultrasound and Computed Tomography**
- Frank H. Miller, MD, Northwestern University, Chicago, IL (lead discussant)

**Evidence-Based Medicine Statements**
1. Ultrasound and CT are best for the late findings of CP but are limited in the diagnosis of early or mild pancreatitis.
2. Intraductal pancreatic calcifications are the most specific and reliable sonographic and CT signs of CP.
3. Computed tomography is helpful for the diagnosis of complications of CP.
4. Computed tomography is helpful for diagnosis of other conditions that can mimic CP.

**Level of Evidence**
1. Conditional recommendation (level of evidence, moderate)
2. Strong recommendation (level of evidence, moderate)
3. Strong recommendation (level of evidence, moderate)
4. Conditional recommendation (level of evidence, low)

The clinical diagnosis of CP, especially in its early stages, can be difficult and frustrating for patients and treating physicians.
Diagnosis of CP by ultrasound and CT imaging relies on changes in morphology of the pancreas, easily detected in the setting of advanced disease, but challenging in early CP. The frequent lack of histopathologic confirmation of the diagnosis further complicates evaluation. The key findings are parenchymal loss (glandular atrophy), chronic inflammation, and fibrosis of the pancreas. Important ductal findings include beading, dilated side-branch radicals, enlargement of the main pancreatic duct (MPD), and dystrophic intraductal calcifications. Transabdominal ultrasound has been used for many years to evaluate the pancreas. Although there have been improvements in hardware and high-resolution transducers, there have not been any recent studies to evaluate the diagnosis of CP using ultrasound. Ultrasound is a noninvasive, inexpensive, and rapid method of evaluating morphological changes in the pancreas; however, considerable limitations reduce its diagnostic utility. Initially, bowel gas and the patient’s body habitus may obscure the pancreas. Assuming adequate visualization, most of transabdominal ultrasound findings are neither specific nor sensitive in the diagnosis of CP. The classic sonographic findings of CP are pancreatic calcifications (Fig. 8). These are seen as multiple echogenic foci in as many as 40% of patients. These foci may or may not shadow based on their size and may show color Doppler twinkling artifact. There is no correlation between exocrine function and the number of calcifications. Late findings seen on ultrasound include alterations of the size and echogenicity of the gland, pancreatic calcifications, pancreatic duct dilatation and irregularity, and biliary dilatation. Ultrasound can be used to visualize pseudocysts and complications of CP, including biliary dilatation and splenic vein thrombosis. Pancreatic parenchymal echogenicity may be normal or decreased in CP, making it an unreliable diagnostic feature.

Computed tomography is considered by many to be the best initial imaging test for CP. It is widely available and allows for comprehensive detailed evaluation of the pancreas. Despite marked improvements in CT, including the development of multiple detector computed tomography (MDCT), there have not been any recent studies evaluating the sensitivity or specificity for CP. The classical CT findings in CP are dilatation of the pancreatic duct, pancreatic calcifications, and parenchymal atrophy. A retrospective study from the Mayo Clinic published in 1989 studied 56 patients with documented CP (Fig. 9). A dilated pancreatic duct and secondary radicals were the most common findings seen in 68% of patients (Fig. 8). Intraductal calcifications were seen in as many as 50% of patients (Fig. 10). These were scattered or clustered, focal, or diffuse. Calcifications develop from deposition of calcium carbonate in inspissated intraductal protein plugs. Calcifications, however, are associated with advanced or severe CP. Other findings include pancreatic parenchymal atrophy (54%), although this is variable and the pancreas can even be enlarged (30%) or normal in appearance (7%), making the diagnosis difficult. Unfortunately, parenchymal atrophy is neither sensitive nor specific and can be seen as a normal aging process. Many patients may have a normal-appearing pancreas on CT despite severe exocrine dysfunction. Other CT findings include MPD dilatation and dilated secondary radicals. The MPD is classically beaded and irregular; however, the main duct may also be regularly contoured. Computed tomography is especially helpful in identifying complications of CP, including pseudocysts, portosplenic venous thrombosis, collaterals and arterial pseudoaneurysms, and pancreaticopleural fistulas. Computed tomography is especially helpful because it can exclude other causes of abdominal pain or weight loss besides CP. In the literature, studies evaluating the CT
features of CP are from the 1980s. Since then, vast improvements in CT technology, including multidetector CT, multiple-phase imaging after contrast enhancement, and thinner collimation, have undoubtedly improved the sensitivity of the diagnosis of CP. Re-evaluation of CP using CT is long overdue.84

It is important to distinguish CP from cancer using imaging studies; however, this is not always possible.90-92 Features that favor CP is intraductal or parenchymal calcifications, lack of obstructing mass, irregular dilatation of the pancreatic duct, and relatively limited atrophy of the gland. The presence of a duct-penetrating sign, which is a dilated duct or branches that penetrate an apparent mass, favors CP (Fig. 13).90 Features favoring cancer include pancreatic duct dilatation with associated mass at the site of obstruction with associated atrophy of the pancreas, vascular invasion, and metastases.

In summary, CT is useful as an initial radiologic test, is helpful to visualize calcifications and duct abnormalities, and excludes other non-CP etiologies for pain or weight loss. In addition, ultrasound and CT are best for the late findings of CP but have limitations, especially in the early diagnosis of mild to CP. Imaging is quite helpful for the diagnosis of complications of CP.

**Topic 4. MRI Imaging**

- Koenraad J. Mortele, MD, Beth Israel Deaconess Medical Center, Boston, MA (lead discussant)

**Evidence-Based Medicine Statements**

1. Compared with ultrasound and CT, MRI is a more sensitive imaging tool for the diagnosis of CP.

Chronic pancreatitis leads to irreversible parenchymal and ductal changes in the pancreas.93 Magnetic resonance imaging may be able to provide an early diagnosis of CP so patients can be treated early on or patients can be applied treatment options that may prevent progression.94 The diagnosis of early CP typically relies on the presence of clinical symptoms, pancreatic exocrine function testing (the criterion standard), and imaging.95 Magnetic resonance imaging is highly sensitive and specific to make the diagnosis of CP by evaluating both parenchymal and ductal changes, especially in patients with more advanced CP.96 However, MRI can also help in the diagnosis of early CP by evaluating the exocrine response of both the ducts and parenchyma after hormonal stimulation of the gland using IV secretin.97-101

When applying a standard MRI/MRCP protocol, radiologists should look, from a ductal perspective, for changes that are induced by the periductal fibrosis, the resultant duct ectasia, and obstructed outflow. These changes of side-branch abnormalities, main duct dilation, and strictures or presence of intraductal stone and intraparenchymal cyst formation can be graded using the Cambridge classification (Fig. 14). In addition to evaluating the ductal changes, MRI is also very sensitive to detect parenchymal abnormalities; what radiologists specifically should look for is subtle signal intensity decreases within the gland, especially on fat-suppressed T1-weighted images.102 It is very important to realize that these parenchymal abnormalities may precede the ductal abnormalities. Therefore, CT or ultrasound may be falsely negative in the detection of early CP because of their lack of detecting subtle ductal abnormalities. These tests fail to depict these parenchymal changes that are only detected with MRI. Another important conventional MRI feature of CP is the delayed and diminished enhancement of the gland after gadolinium chelates administration. Therefore, in summary for conventional MRI/
MRCP, the parenchymal features of CP include, in addition to atrophy (Fig. 15), abnormal decreased signal intensity on the fat-suppressed T1-weighted images (Fig. 16) and delayed and limited enhancement after contrast administration (Fig. 17).

As mentioned previously, one could currently explore the MRI appearances of early CP after hormonal stimulation of the pancreas, using IV secretin, and look for new or improved detection of ductal and parenchymal abnormalities (Fig. 18). One's primary assessment in evaluating the pancreas with secretin-enhanced MRCP should focus on the pancreatic duct compliance, which defines a normal distention (of approximately 1 mm) of the ducts after secretin stimulation and then a recovery of the duct diameter to baseline (10 minutes after IV secretin injection). Several investigators have evaluated the time to peak MPD dilation after IV secretin stimulation to differentiate a normal pancreas from a pancreas in patients who have CP. Patients with early CP may have completely normal conventional MRCP/MRI studies, and only the secretin stimulation will depict the mild abnormal pancreatic ductal compliance. Furthermore, one should also evaluate the IV secretin-augmented MRCP images for increased number of side branches or new recognition of side branches and evaluate the exocrine pancreatic function by assessing the production and excretion of bicarbonate and fluid by the gland. The latter can be evaluated both quantitatively and semiquantitatively. Semiquantitatively, one can use a rudimentary grading system that evaluates the filling of the duodenal and jejunal loops of bowel after stimulation. A much more accurate way is to actually measure the exact amount of fluid that gets produced by the gland using a multislice fast T2-weighted sequence and a very simple mathematical model. Measuring the signal intensity of the fluid and the 3-dimensional area of fluid before and after the stimulation of the pancreas with IV secretin allows measuring how much fluid is being produced by the gland over time and can provide a flow rate chart. This quantitative model has been used successfully to evaluate the exocrine fluid flow rate in patients with CP before and after secretin administration.

Lastly, some future MRI applications are on the horizon that may have immediate impact on the way we image patients with CP. The more universal use of high field strength magnets now allows for increased signal-to-noise in the pancreas, and using those high field strength magnets, we can depict more subtle abnormalities in the pancreas compared with lower field strength magnets. Perfusion MRI explores that fact that the pancreas in patients with CP has decreased and delayed enhancement and aims to detect subtle alterations in pancreatic parenchymal perfusion. Diffusion-weighted MRI measures the restriction of free Brownian motion (diffusion) of water molecules in the gland. The more fibrosis there is, the more likely there will be less diffusion of water molecules (the latter is measured as apparent diffusion coefficient); therefore, apparent diffusion coefficient values will be lower in patients with CP than in normal patients. Exploiting this idea, one can actually evaluate the gland using diffusion MRI after IV secretin stimulation and enhance the sensitivity to depict subtle abnormalities in diffusion restriction and separate normal patients from those with early CP.

In summary, MRI is a great tool to detect ductal and parenchymal changes in CP patients, both at baseline or after stimulation of the pancreas with secretin.
stimulation with IV secretin. The complexity of the disease, however, remains challenging and limits the accuracy of MRI. Ductal changes may be preceded by parenchymal changes and vice versa. Additional findings can only be detected if one stimulates the gland with IV secretin. There probably is a need for an EUS-like MRI-based staging system, which does not exist at this point, combining the ductal changes with the parenchymal changes and with the findings after IV secretin stimulation.

**Topic 5. Endoscopic Ultrasound**

- Michael J. Levy, MD, Mayo Clinic Rochester, Rochester, MN (lead discussant)

**Evidence-Based Medicine Statements**

1. The ideal threshold number of EUS criteria necessary to diagnose CP has not been firmly established, but the presence of
5 or more and 2 or less strongly suggests or refutes the diagnosis of CP.

2. The EUS features of CP are not necessarily pathologic and may occur as a normal aging, as a normal variant, or due to nonpathologic asymptomatic fibrosis in the absence of endocrine or exocrine dysfunction.

3. The relatively poor interobserver agreement (IOA) for EUS CP features limits the diagnostic accuracy and overall utility of EUS for diagnosing CP.

**Level of Evidence**

1. Strong recommendation (level of evidence, low)
2. Strong recommendation (level of evidence, low)
3. Strong recommendation (level of evidence, moderate)

Endoscopic ultrasound is an often used diagnostic tool for evaluating CP due to the ability to visualize subtle alterations in pancreatic structure before other imaging modalities and functional tests are abnormal. Although the EUS sensitivity is enhanced as one lowers the necessary number of criteria for diagnosis, the already poor specificity further decreases, often leading to unnecessary and often risky interventions. Some have even performed total pancreatectomy and auto-islet cell transplant for pain secondary to presumed CP, only to find normal histology in the resected specimen.

The EUS diagnosis is based on ductal and parenchymal criteria described by the International Working Group using minimum standard terminology, and the criteria have been linked to distinct pathologic correlates identified on histological examination (Fig. 19). Although the minimum standard terminology system classically lists 9 potentially abnormal features, others also consider 2 additional features including an enlarged pancreas and narrowing of the pancreatic duct. The number of EUS criteria needed to diagnose CP varies among endosonographers and institutions (Table 4).

The ideal threshold number of EUS criteria necessary to diagnose CP has not been firmly established. For patients with no pancreatic pathology and those with severe CP, EUS provides reliable and accurate diagnosis. However, the diagnosis is seldom in doubt for such patients. Endoscopic ultrasound offers the greatest potential to impact patient care in persons with early or mild CP; however, it is in this subset of patients that results are most uncertain and unreliable. Previously, there was broad agreement that the presence of 5 or more features reliably establishes the diagnosis of CP and that absence of all features reliably excludes CP.

However, given that some EUS features are actually physiologic and others pathologic, the 5 criteria threshold may not be appropriate. It has been suggested that the presence of 1 to 2 EUS features should be regarded as a normal gland and that the presence of 3 to 4 criteria may indicate early or mild CP. Diagnosing CP based solely on minimal EUS criteria, with otherwise negative or inconclusive findings, is strongly discouraged. It is important to correlate the EUS findings with clinical, structural, and functional analyses in this group of patients with possible early or indeterminate disease.

Pancreatic injury is a progressive process that leads to increasing structural abnormalities and functional deficits over time. The degree of injury necessary to designate CP is not clearly defined. Although exocrine pancreatic insufficiency in the form of steatorrhea does not typically occur until 70% to 90% or more of functional capacity is lost, the occurrence, timing, and severity of disease manifestations greatly vary. Our goal was to accurately diagnose early CP to allow effective intervention to positively influence the natural disease course. However, there is a paucity of data confirming the impact of any currently available therapies or interventions. Efforts to enhance early diagnosis are typically associated with overdiagnosis and decreased diagnostic specificity. Given the limited impact of early interventions and risk of delivering unnecessary and risky care, most set test parameters to favor a greater positive predictive value at the cost of a somewhat delayed diagnosis.

Many have questioned the predictive value of individual EUS criteria and suggested their respective predictive values may differ significantly. Rajan et al evaluated 120 patients without evidence of pancreatic disease who underwent EUS for a nonpancreatobiliary indication. They identified at least 1 parenchymal and/or ductal EUS abnormality in 28% of patients, with a trend toward increasing numbers of abnormal features with ages younger than 40 years (23%), 40 to 60 years...
and older than 60 years (39%) (P = 0.13). Hyperechoic stranding (n = 22) was the most common finding in all age groups. They concluded that ductal or parenchymal calculi, duct narrowing, duct dilatation, or the presence of more than 3 features seemed to be the most specific features for diagnosing CP regardless of age. Others have reported similar findings.\(^{123,126}\)

The Rosemont classification was developed from a consensus conference that included 32 internationally recognized endosonographers.\(^{127}\) Participants defined each EUS CP criterion and applied these features in a manner that was felt to optimize the diagnostic accuracy. Major and minor criteria were developed and subdivided into major A and major B because of a perceived difference in predictive accuracy. Parenchymal major A criteria included hyperechoic foci with shadowing and well-circumscribed lobularity, and the only ductal major A criteria was MPD calculi. The only parenchymal major B criteria was lobularity with honeycombing. Minor parenchymal criteria were cysts, stranding, nonshadowing hyperechoic foci, and lobularity with noncontiguous lobules. Minor ductal criteria were dilated ducts (body \(\geq 3.5\) mm and tail \(\geq 1.5\) mm), irregular MPD contour, dilated side branches 1 mm or more, and hyperechoic duct margin. The diagnosis of CP based on the Rosemont Classification was consistent if one of the following was present: (a) 1 major A feature + \(\geq 3\) minor features, (b) 1 major A feature + major B feature, and (c) 2 major A features. All other combinations of features were categorized as suggestive, indeterminate, or normal. Although this classification system represents an important step forward due to the use of weighted criteria, their findings were based solely on expert opinion.

It is uncertain that EUS features are pathologic, normal age-related findings, normal anatomic variants, or due to nondiagnostic asymptomatic fibrosis in the absence of endocrine or exocrine dysfunction.\(^{125}\) Such asymptomatic fibrosis has been reported in alcoholism, advanced age, male gender, obesity, and cigarette smoking. These features have been associated with abnormal pancreatic imaging and histology in patients without evidence of

<table>
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<th>EUS Criteria for CP and Histological Correlates(^{91-93})</th>
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<tr>
<td><strong>EUS Criteria</strong></td>
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<td>Parenchymal features</td>
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<td>Hyperechoic foci</td>
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<td>Hyperechoic strands</td>
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CP and are reported in as many as 60% of alcoholics without clinical evidence of CP. Although some of these patients may have mild disease destined to increase in severity over time, the lifetime risk of CP in alcoholics is only 2% to 5%, far less than the presence of fibrosis alone. Endoscopic ultrasound findings must be interpreted with caution due to the inability to distinguish this clinically and metabolically benign asymptomatic fibrosis from true CP.

One of the greatest limitations in the use of EUS for evaluating CP is the relatively poor IOA. Wallace et al. studied the interpretations from 11 expert endosonographers, blinded to clinical information, who evaluated videotaped examinations for the presence of 9 CP criteria among 33 patients with CP. Although agreement was good in 2 features, duct dilatation (κ = 0.6) and lobularity (κ = 0.51), agreement was poor for the other 7 features (κ < 0.4). There was moderate overall agreement for the final diagnosis of CP (κ = 0.45). Topazian et al. assessed IOA for interpretation of EUS in persons at high risk for pancreatic cancer using recorded video clips and found similar results.

In summary, although EUS is an important diagnostic tool for evaluating many gastrointestinal and nongastrointestinal disorders, the same may not be true for suspected CP. Despite advances in EUS technology and training, there has been no meaningful progress in EUS-based diagnosis since initial reports. The limitations of EUS are greatest for patients within the early/indeterminate CP and definite CP diagnostic range (>2 to <5). Definitive diagnosis in this vulnerable patient population must include pancreas function testing and advanced radiologic imaging such as MRI and secretin-enhanced MRCP. Further study is needed to refine the definitions of EUS features of CP, to determine the relative predictive value of each feature, to establish an ideal threshold number of criteria, and to consider the composite results in a manner that optimizes their diagnostic and prognostic utility. We must also improve our understanding of the impact of factors such as aging, obesity, and smoking on imaging. Any meaningful advance in the use of EUS will mandate broader reproducibility in image interpretation and improved IOA. If we are to err in the use of EUS, we should do so in a manner that favors more stringent diagnostic criteria to avoid overdiagnosis and delivery of unnecessary and potentially risky therapies. This approach will lead to failed diagnosis in some patients but is favored given the current lack of reliable effective therapies.

### Evidence-Based Medicine Statements

1. Endoscopic retrograde pancreatogram (ERP) is rarely used for diagnostic purposes.
2. The correlation between the Cambridge criteria and histology is highest in advanced CP.
3. Multiple confounders limit the interpretation of ductal changes by Cambridge criteria.

### Level of Evidence

1. Strong recommendation (level of evidence, moderate)
2. Strong recommendation (level of evidence, moderate)
3. Strong recommendation (level of evidence, low)

With the widespread availability of cross-sectional imaging (CT and MRI) and EUS, ERPs are rarely, if ever, used to diagnose CP, and instead, they have largely been relegated to a therapeutic procedure. Endoscopic retrograde pancreatogram has been utilized to identify ductal abnormalities or obstructions, to clarify ductal anatomy before surgical intervention, and to confirm the patency of postoperative anastomoses, including pancreaticogastrostomies. Now recent guidelines, published by the American Society for Gastrointestinal Endoscopy (ASGE) in 2006, recommend that ERP should be reserved for patients in whom the diagnosis still remains unclear after pancreatic function testing (PFT) or other noninvasive (CT or MRI) or less invasive imaging studies (EUS) have been performed.

The diagnosis of CP by ERP is made on the basis of changes in the MPD and side branches, requiring a quality pancreatogram to most accurately delineate the ductal anatomy. Contrast should be injected through the length of the pancreatic duct to the tail, as well as into the secondary branches while avoiding acinarization of contrast. It is also important to avoid intra-ductal air bubbles and movement artifact, which will contribute to misinterpretation of the pancreatogram.

The most accepted criteria for scoring ductal changes on pancreatograms are the Cambridge criteria, which grade pancreatograms from normal to equivocal to mild, moderate or severe CP based on main duct and side-branch abnormalities (Fig. 20B–E). Main duct abnormalities include dilation, narrowing, strictures, filling defects, and leaks or cavities. Identification of these abnormalities can be subjective as their definitions are not clear. Average normal main duct diameters were 3.6, 2.7, and 1.6 mm in the head, body, and tail respectively, although the upper limit of normal may be as high as 6.5, 5, and 3 mm in the head, body, and tail, respectively. Main duct dilation is either general (involving more than two thirds of the main duct) or local (less than two thirds of the ducts). Severe dilation was defined as being more than 1 cm. Side-branch abnormalities include decreased number, shortened length, and dilated or narrowed caliber; however, the criteria to distinguish normal from abnormal are not clearly defined.

There are several limitations that account for the decline in the use of ERP for diagnostic purposes. The ERP procedure is invasive and carries a risk of postprocedure complications, including AP. Endoscopic retrograde pancreatogram can be operator dependent, and the interpretation of pancreatograms is subject to interobserver variability. Moreover, pancreatograms allow visualization of the ductal anatomy only, without any parenchymal imaging. Other potential confounders to interpretation of pancreatograms include age-related ductal changes, post-AP ductal changes, and Pancreatic Intraepithelial Neoplasia (PanIN)-related branch duct changes, which are indistinguishable from ductal changes related to CP.

The experts at the Cambridge conference admitted that pancreatography “does not imply coincidence with the severity of disease pathology or functional status.” A recent study of 31 patients who underwent both ERCP and pancreatic resection showed a correlation between the Cambridge criteria and histology in 74% (n = 23). This correlation between pancreatogram and histology was higher in patients with moderate and marked disease (77%) by ERP than those with normal or equivocal, or mild changes (67%). In a postmortem study of 69 patients without CP, pancreatic duct abnormalities on pancreatograms led to a diagnosis of CP in 81% of the patients (minimal 37%, moderate 33%, severe 11%). Therefore, considering ductal abnormalities alone can lead to a misdiagnosis of CP. In correlation with other tests, there is good correlation between ERP and MRCP. The correlation with PFT may be modest, particular with early disease, and is the subject of a later discussion.

In summary, ERP can yield useful diagnostic information though it is rarely used as a diagnostic modality in CP. The
correlation of abnormalities on pancreatogram with histology and function is higher in advanced disease than early disease.

**Topic 7. Indirect Pancreatic Function Testing**

- John G. Lieb, II, MD, University of Pennsylvania, Philadelphia, PA (lead discussant)

**Evidence-Based Medicine Statements**

1. Indirect PFTs generally are sensitive for steatorrhea and useful in quantifying the degree of exocrine insufficiency.
2. Indirect PFTs are moderately sensitive and specific for diagnosing advanced CP but are less so for diagnosing early CP.
3. The fecal elastase assay, the polyclonal assay more than the monoclonal, can be limited in specificity, especially if the stool sample is watery and/or in the presence of small bowel disease.
4. Fecal chymotrypsin may be useful in detecting compliance with exogenous pancreatic enzyme supplementation.
5. Fecal fat assays are sensitive for steatorrhea but are of limited utility due to the cumbersome nature of patient collection and laboratory handling of samples. In addition, strict adherence to dietary recommendations for several days is required.

**Level of Evidence**

1. Conditional recommendation (level of evidence, low)
2. Conditional recommendation (level of evidence, strong)
3. Conditional recommendation (level of evidence, low)
4. Conditional recommendation (level of evidence, low)
5. Conditional recommendation (level of evidence, moderate)

Indirect PFTs, such as serum trypsinogen, fecal elastase, and fecal fat measurements, do not require direct hormonal stimulation of the pancreas. Typically, indirect PFTs are sensitive only for late CP (when steatorrhea is already present). Thus, they are best used to quantify the degree of insufficiency.
in established CP, rather than diagnosing CP. For example, indirect PFTs are modestly sensitive and specific even for advanced CP. In general, indirect tests of pancreatic function should always be accompanied by cross-sectional CT or MRI imaging studies to rule out malignancy.

In rare circumstances when direct PFT may not be available or tolerated, indirect PFTs may be used to assist in the diagnosis of CP. In this setting, it is crucial to understand the characteristics of the type of assay being used (serum trypsin by radioimmunoassay (RIA) vs enzyme-linked immunosorbant assay (ELISA) and monoclonal vs polyclonal fecal elastase assays) and whether the patient has complied with pretesting preparations (high-fat diet for fecal fat measurement, etc). Laboratory factors also play a role, for example, a fecal elastase test should be performed on a solid stool sample to avoid falsely positive results. Serum amylase and lipase measurement should not be entirely discounted as a potentially useful indirect test of pancreatic function, especially if they have a low value.

Typically when performing indirect tests to diagnose CP, the reference values should likely meet a more stringent threshold than when performed in patients with established/obvious CP. In this setting, at least 2 indirect PFTs, sampling different substrates (blood, stool), should be performed. For example, a serum trypsin measured by RIA of less than 20 pg/dL and a fecal elastase less than 50 μg/dL stool by monoclonal antibody in the same patient are probably diagnostic of CP, although further study is needed in this area. Classic false-positive fecal elastase measurements (low levels) occur in small bowel bacterial overgrowth and watery stool. Conversely, classic false-negative serum trypsin measurements (normal/high levels) occur when performed in the setting of AP inflammation. In the absence of other supporting evidence, intermediate indirect PFT results (monoclonal fecal elastase 50–200 μg/dL or trypsin 20-29 pg/dL by RIA) should be interpreted with caution when used to diagnose CP. A polyclonal fecal elastase may be a better test; however, the monoclonal assay is currently better standardized, yet some large ultrasound commercial reference laboratories reflexively use the polyclonal assay. Newer methods such as 13C-MTG triglyceride breath testing, although shown to be sensitive and specific in select tertiary referral centers, have not yet been universally adopted in the United States.

Fecal fat measurement alone is highly nonspecific and in isolation cannot diagnose CP. Exocrine pancreatic insufficiency (steatorrhea) in the setting of established CP is currently defined as more than 7 g of fat per 24 hours measured by a 72-hour fecal fat test. This reference value is valid only in the appropriate clinical context; small bowel bacterial overgrowth and celiac sprue/short gut and inflammatory bowel disease have been excluded. A positive qualitative fecal fat (more than 6 droplets per high power field), which is a fairly insensitive test for steatorrhea, or monoclonal fecal elastase (<50 μg/dL) under similar circumstances would also support the diagnosis of exocrine insufficiency. Fecal chymotrypsin is currently only available through 1 company in the United States; however, because it detects porcine pancreatic elastase, it may be useful to evaluate patient compliance with exogenous pancreatic enzyme supplementation.

The role of tests of endocrine function such as a serum pancreatic polypeptide level, other than traditional definitions of diabetes such as a hemoglobin A1C, a fasting glucose, or
The endoscopic PFT (ePFT) has good correlation with the traditional secretin and cholecystokinin (CCK) PFTs certainly will miss patients with less severe pancreatic damage and therefore has a high sensitivity for late CP, but it may be limited by, among other factors, false positives for secretory dysfunction in patients with at least 30% pancreas damage. Direct PFT is capable of detecting back to the early 1900s to newer techniques, including the endoscopically assisted and the purely endoscopic methods. Direct PFT may be limited by, among other factors, false positives for at least several months after a bout of AP and false negatives in some patients who have early CP. Direct PFT is capable of detecting secretory dysfunction in patients with at least 30% pancreas damage and therefore has a high sensitivity for late CP, but it certainly will miss patients with less severe pancreatic damage.

Sensitivity of the traditional Dreiling tube test for early CP decreases to 70% to 75%.147,171,172 The original secretin-stimulated direct PFT was performed with the Dreiling tube and popularized at the University of Florida (Fig. 21). This test is highly accurate and measures duct cell function. This double lumen, 26F oroduodenal tube with both gastric and duodenal ports is introduced using fluoroscopy guidance. The patient's oropharynx is medicated with topical anesthesia. Under fluoroscopic guidance, the weighted tip of the Dreiling tube is swallowed and advanced close to the ligament of Treitz and the tapered radiopaque portion of the tube is positioned at the pylorus. Low, constant suction is applied to collect duodenal fluid at 0, 15, 30, 45, and 60 minutes after an IV bolus injection of secretin, and the fluid is analyzed for pH, volume, and bicarbonate concentration. Drawbacks of this procedure may include patient discomfort, need for fluoroscopy, and limited availability of the traditional Dreiling tubes. Patients with nausea, gastroparesis, and pyloric stenosis pose a challenge to performing this procedure.

Another direct PFT is the CCK PFT developed at the Mayo Clinic, which is a dual tube technique using 2 double lumen tubes for perfusion and aspiration of both gastric and duodenal contents. This test measures acinar cell function. This test incorporates a marker perfusion system to account for the amount of gastric and duodenal fluid that is “lost” or escapes aspiration into the distal small bowel lumen to accurately calculate the total pancreatic enzyme secretory output. Disadvantages of this procedure include limited availability of the special “dual tube” system, need for fluoroscopy, utilization of a PEG/mannitol marker, and need for continuous IV CCK infusion during the duration of the test.173 Combining secretin and CCK injection does not seem to yield improved results, and in fact, peak bicarbonate concentration over 1 hour is the best correlate to histologic findings.

Several endoscopic variations of pancreas function testing have been developed.174–180 The pure ePFT developed at the Cleveland Clinic allows the patient to be moderately sedated, typically with a long-acting benzodiazepine and narcotic, for the upper endoscopy while pancreas fluid is suctioned via the upper esophagogastroduodenoscopy (EGD) or EUS endoscope.175 After IV bolus injection of secretin (0.2 μg/kg), duodenal fluid is aspirated from the duodenal bulb. When performing ePFT, it is important to completely aspirate gastric secretions to avoid contamination of duodenal fluid by the acidic gastric contents. Placing the patient at a 30-degree angle or in Trendelenburg position prevents distal migration and loss of duodenal fluid. It is also very important to aspirate and discard approximately 2 to 4 mL of duodenal fluid before each collection to rinse residual gastric fluid from the suction channel. For the full 1-hour test, normal peak bicarbonate level is greater than or equal to 80 mEq/L. The shortened screening test uses a peak bicarbonate cut point of 75 meq/L. Advantages of this test include its simplicity, universal availability of upper

**FIGURE 23.** New Dreiling tube.

**FIGURE 24.** Ligury drainage tube (Burton method).
endoscopy, and lack of need for fluoroscopy. Although modest sedation does not affect ePFT results, the impact of heavy sedation and/or general anesthesia on ePFT results is unclear and may confound function test result interpretation.176 There is good correlation between the traditional Dreiling test and the ePFT test (Fig. 22). A newer disposable latex-free version of the Dreiling tube can also be endoscopically placed over a guide wire with fluoroscopic assistance (Fig. 23), whereas the Liguory tube (Frank Burton method) can be advanced over a wire during upper endoscopy without fluoroscopy.179 The disposable Liguory tube has a pigtail tip with side ports at the end (Fig. 24). After the placement of the tube, the patient is transferred to the recovery area where secretin is administered and PFT is performed. The average time for endoscopic Dreiling tube placement is approximately 10 minutes in combination with 2 minutes of fluoroscopy time. Intraductal PFT performed during ERCP requires cannulation of the pancreatic duct followed by injection of secretin, and aspiration of pancreatic secretions from within the pancreatic duct for approximately 15 minutes. After secretin injection, the bicarbonate level in pancreas fluid continues to rise and does not plateau for about 15 to 30 minutes (Fig. 22). Therefore, timing of aspirations is critical for accurate functional assessment. A recent study comparing intraductal PFT during ERCP to the standard Dreiling test reported a 20% specificity and 80% sensitivity for the intraductal test.180

In summary, the 1-hour ePFT and Dreiling tube collection methods are the nonhistologic criterion standards for diagnosis of early CP. A shortened 30- to 45-minute ePFT test may be used to screen for CP. In practice, patients referred with chronic abdominal pain undergoing evaluation for early CP may undergo screening for CP using EUS combined with the shortened 45-minute ePFT to assess for both structural and functional changes of CP. Because the 45-minute test has slightly lower specificity than the full 1-hour test, patients with borderline results should undergo a full 1-hour PFT with the endoscopic or Dreiling tube method.

**Topic 9. Correlation of Imaging and Function With Histology**

- Tyler Stevens, MD, Cleveland Clinic, Cleveland, OH (lead discussant)

**Evidence-Based Medicine Statements**

1. As structural severity worsens in CP, exocrine function declines.
2. Both EUS and PFT results correlate with fibrosis in CP.
3. A combined approach (eg, EUS/ePFT) could improve detection of minimal change CP (MCCP).

**Level of Evidence**

1. Strong recommendation (level of evidence, moderate)
2. Conditional recommendation (level of evidence, low)
3. Conditional recommendation (level of evidence, low)

Mild exocrine insufficiency is frequently present in mild and severe CP, and progressive structural fibrosis is reflected in exocrine function decline. However, this relationship is not linear, and imaging and PFT results are not perfectly concordant.
Multiple studies have shown suboptimal concordance of ERCP and PFT results, with the greatest discrepancy in mild disease. In 1 example, the concordance rate for secretin PFT and ERCP in noncalcific CP was only 47%. Endoscopic ultrasound is now favored over ERCP for the endoscopic diagnosis of CP due to increased safety and the ability to evaluate both the ductal and parenchymal architecture. As with ERCP, similar discordance has been seen between EUS criteria and PFT results. The overall concordance rates between EUS and secretin PFT range from 48% to 70% in 3 past studies comparing EUS and secretin PFT. In 302 patients undergoing a combined EUS and secretin endoscopic PFT, a moderate correlation was observed between peak bicarbonate concentration and EUS score ($r = -0.59$).

Only a few recent studies evaluating ERCP, EUS, and PFT have incorporated histological reference standards. Two studies compared secretin and cholecystokinin PFT results with histological fibrosis. Twenty-five patients underwent a PFT before surgery for painful CP. A discriminative analysis revealed moderate correlations of certain PFT parameters (eg, peak bicarbonate and trypsin concentrations) with specific histological features (eg, atrophy, small duct dilation). Weaker correlations were observed between other parameters. Another study compared PFT results with pancreatic histology in 108 patients undergoing a variety of abdominal surgeries. Most patients had surgery done for nonpancreatic indications (eg cholecystectomy) that included performance of a wedge biopsy of the pancreas. A significant correlation ($r = 0.59$) was observed between the overall PFT and histological rating scales.

Three recent studies have compared preoperative EUS criteria with histology in patients undergoing pancreatic resections or operative biopsy, using the pancreatic fibrosis score of Ammann et al. These studies differ in the patient populations (CP vs pancreatic masses) disease severity (minimal change vs calcific) and the fibrosis score cut point used to diagnose CP. The overall correlation coefficients for EUS versus fibrosis scores range from 0.40 to 0.85, suggesting a moderate to very good correlation. The sensitivity and specificity estimates for EUS compared with the histological reference standard range from 83% to 91% and 80% to 100%, respectively. Another study reported preoperative EUS results in 50 patients undergoing total pancreatectomy with autologous islet cell transplant. One to 3 wedge biopsies were obtained for histological examination before enzymatic digestion of the gland for islet cell isolation. The histological findings of fibrosis, atrophy, or inflammation were considered individually diagnostic of CP. This study was less encouraging for EUS as a diagnostic test. Compared with histology, the area under the receiver operating characteristics curve was only 0.593, indicating poor discrimination. Furthermore, the negative and positive predictive values were poor even when the EUS cut point was optimized for each.

It is controversial whether EUS or PFT is most sensitive for detecting early CP. It is clear that some patients with significant structural changes have preserved exocrine function, whereas others have minimal or no EUS features and might still have an abnormal PFT indicating early CP. In a recent study, EUS and/or a secretin endoscopic PFT were done in 25 patients within 1 year of resection or open biopsy. Twelve patients had both tests done and had histological fibrosis indicating CP. Correlations for EUS and ePFT were 0.72 and 0.57, respectively (Fig. 25). Of these, all 25 had either an abnormal EUS or ePFT, indicating 100% sensitivity of the combined approach (Fig. 26). Although the sample size is small, these results imply that combining structural with function testing may optimize the detection of MCCP.

![FIGURE 27. STEP-wise algorithm approach to diagnosis of CP.](https://example.com/fig27)

- **Step 1:** survey—data review, risk factors, CT imaging.
  - CT Scan
  - CP Diagnostic criteria: calcifications in combination with atrophy and/or dilated duct
  - Diagnostic criteria met, no further imaging needed
  - Inconclusive or nondiagnostic results, continue to Step 2

- **Step 2:** secretin MRCP
  - MRU/MRCP with secretin enhancement (sMRCP)
  - CP Diagnostic criteria: Cambridge Class III, dilated duct, atrophy of gland, filling defects in duct suggestive of stones
  - Diagnostic criteria met; no further imaging needed
  - Inconclusive or nondiagnostic results, continue to Step 3

- **Step 3:** EUS with quantification of parenchymal and ductal criteria
  - CP Diagnostic criteria: ≥ 5 UES CP criteria
  - Diagnostic criteria met; no further imaging needed
  - Inconclusive or nondiagnostic results; continue to Step 4

- **Step 4:** PFT (with secretin)—gastrroduodenal (SSST) or endoscopic (ePFT) collection method
  - CP Diagnostic criteria: peak [bicarbonate] <80 meq/L
  - Diagnostic criteria met; no further imaging needed
  - Inconclusive or nondiagnostic results; continue to Step 5
  - **Note:** Consider combining ePFT with EUS

- **Step 5:** ERCP
  - CP Diagnostic criteria: Cambridge III, Dilated main pancreatic duct and greater than 3 dilated side branch
  - Diagnostic criteria met; no further imaging needed
  - Inconclusive or nondiagnostic results require monitoring of signs and symptoms and repeat testing in 6 months-1 year

**Chronic Pancreatitis**
In summary, the overall correlation of EUS and PFT with histology seems to be in the moderate to very good range. The studies comparing EUS and PFT with histology have significant limitations. Most were done using a highly selected sample of patients undergoing planned pancreatic surgery. The studies are heavily weighted with severe disease, which may falsely elevate sensitivity (ie, spectrum bias). In addition, not all patients undergoing the EUS or PFT go on to receive a histological diagnosis, which produces verification bias. The use of wedge pancreatic biopsies in some studies may lead to sampling bias. A combined EUS/ePFT approach may be most useful for the evaluation of patients with chronic abdominal pain and suspected early or MCCP.

Summary of Diagnostic Guidelines in CP

- Darwin L. Conwell, MD, MS, Ohio State University Wexner Medical Center, Columbus, OH (lead discussant)

Confirming a diagnosis of CP is clear in highly suspicious patients (recurrent pancreatitis, alcohol or smoking abuse) with steatorrhea, weight loss, and marked/moderate morphologic changes in the gland. The diagnosis of CP still remains challenging in early stages (equivocal and mild morphologic or physiologic changes) of the disease.9,10 These patients should not be classified as having CP until definitive diagnostic features are evident. Our guidelines propose a diagnostic algorithm that proceeds from a noninvasive to more invasive diagnostic approach.

### TABLE 5. Diagnostic Evidence for CP Diagnosis

<table>
<thead>
<tr>
<th>Evidence</th>
<th>Criteria</th>
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</table>
| Definitive evidence (any of the following) | Moderate/marked pancreas imaging morphology (ie, ductal and parenchymal abnormalities)  
Pancreatic calcifications  
Histologic confirmation |
| Probable evidence (abnormal imaging/suggestive history + abnormal physiology) | Mild pancreas imaging morphology  
or  
Recurrent pseudocyst/pancreatitis plus  
Abnormal pancreas physiology (secretin test, diabetes, steatorrhea) |
| Insufficient evidence | Equivocal pancreas imaging morphology  
or  
Abdominal pain with any of the following:  
No history of pancreatitis (lipase < 3 × upper limit of normal (ULN)  
Normal imaging  
Family history of pancreatitis  
Prior ERCP with pancreatic duct stenting  
Presence of TIGAR-O risk factors (smoking, alcohol) |

Evidence should be interpreted in a patient with history and physical examination suspicious for CP such as abdominal pain, history of AP, steatorrhea responsive to pancreatic enzyme replacement therapy, heavy alcohol or smoking history, and genetic risk factors of family history.

### TABLE 6. Pancreas Morphology Imaging Grade (I–IV)

<table>
<thead>
<tr>
<th>Ultrasound</th>
<th>Equivocal (I)</th>
<th>Mild (II)</th>
<th>Moderate (III)</th>
<th>Marked (IV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT/MRI scan</td>
<td>1 of the following: main duct enlarged (2–4 mm), slight gland enlargement, heterogeneous parenchyma, small cavities (&lt;10 mm), irregular ducts, focal pancreatitis, increased echogenicity of main duct wall, irregular head/body contour</td>
<td>≥2 of the following: enlarged main duct (2–4 mm), gland enlargement, heterogeneous parenchyma, small cavities (&lt;10 mm), irregular ducts, focal AP, increased echogenicity of main duct wall, irregular head/body contour</td>
<td>Cannot distinguish from mild</td>
<td>Moderate changes plus ≥1 of the following: large cavities (&gt;10 mm), gland enlargement, intraductal filling defects/calculi, duct obstruction, stricture or gross irregularity</td>
</tr>
<tr>
<td>EUS (0–9 criteria standard criteria)</td>
<td>0–2</td>
<td>3–4</td>
<td>≥5</td>
<td></td>
</tr>
<tr>
<td>MRCP/ERCP</td>
<td>&lt;3 Abnormal side-branch changes</td>
<td>≥3 Abnormal side-branch changes</td>
<td>Abnormal main duct; &gt;3 abnormal side branches</td>
<td>Moderate changes plus; 1 of the following: obstruction, filling defects, severe irregularity/dilation of main duct</td>
</tr>
</tbody>
</table>
approach (Fig. 27A–B). This algorithm maximizes specificity (low false-positive rate) in subjects with chronic abdominal pain and equivocal imaging changes. The diagnosis of CP is made based on definitive criteria. All patients with suspected CP should have a dedicated pancreatic protocol CT scan or MRI/MRCP to rule out pancreas carcinoma.

Our guidelines define the diagnostic evidence for CP as definitive, probable, and insufficient based on current knowledge of the natural history of the disease (Table 5). Without sufficient evidence, patients should not be mislabeled as having CP, when in fact they may have chronic abdominal pain syndrome and a remote history of ERCP-induced pancreatitis or ductal changes. Given there is no current therapy to alter disease progression, it is better to err on the side of not labeling the patient with CP. In most cases, longitudinal follow-up is recommended with serial imaging and physiologic testing in equivocal/mild cases with insufficient evidence of CP until definitive evidence is apparent.

Once a diagnosis of CP is confirmed, our guidelines recommend a comprehensive characterization of CP in regards to etiology (TIGAR-O; see Table 2), morphology (modified from Mannheim group, Table 6), and physiologic state (Table 7). In an attempt to standardize research studies across centers, a nomenclature is proposed (Table 8). To conclude, case studies are presented.

### TABLE 8. APA CP Nomenclature

In an attempt to combine the latest diagnostic criteria into a working nomenclature that incorporates etiology, morphology, and physiologic status, we propose the following nomenclature for CP once probable or definitive evidence is present:

<table>
<thead>
<tr>
<th>Stage</th>
<th>Physiologic Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Normal secretory, exocrine, and endocrine function</td>
</tr>
<tr>
<td>B</td>
<td>Secretory dysfunction (abnormal secretin stimulation test)</td>
</tr>
<tr>
<td>C</td>
<td>Exocrine insufficiency (abnormal fecal elastase, steatorrhea, low serum trypsin)</td>
</tr>
<tr>
<td>D</td>
<td>Endocrine insufficiency (abnormal fasting glucose, glycohemoglobin, glucose tolerance test)</td>
</tr>
<tr>
<td>E</td>
<td>Both C and D</td>
</tr>
<tr>
<td>X</td>
<td>Not classified/unknown</td>
</tr>
</tbody>
</table>

### TABLE 9. CP Case Studies

Diagnosis case 1: insufficient evidence. A 35-year-old woman with chronic narcotic requiring abdominal pain. A CT scan is normal without evidence of a pancreatic mass. MRI/secretin-enhanced MRCP is normal. Pain is similar to ERCP-induced pancreatitis pain. No history of pancreatitis before or after resolution of ERCP-induced AP. Stool fecal elastase is >500 μg/g on a solid sample. Tertiary referral center EUS has 3 criteria, and ePFT has a peak bicarbonate of 83 meq/L.

Diagnosis: chronic abdominal pain syndrome

Diagnosis case 2: probable evidence. A 56-year-old male smoker with history of alcohol abuse 10 years earlier who presents with intermittent abdominal pain and mild lipase enzyme elevations to 2×ULN. Computed tomography scan is negative for pancreas mass. Fecal elastase is 225 μg/g on a solid stool sample. MRI shows decreased T1 signal, and secretin-enhanced MRCP reveals a few prominent side branches. EUS shows 4 criteria, and ePFT has a peak bicarbonate of 69 meq/L.

Diagnosis: chronic alcohol-induced pancreatitis, imaging grade II, physiology stage B

Diagnosis case 3: definitive evidence. A 33-year-old woman with acute onset of severe AP. No prior history or use of alcohol or drugs. Computed tomography scan consistent with interstitial pancreatitis without a pancreatic mass. Her father had a pancreaticojunostomy when he was 25 years old for recurrent pancreatitis. Further testing reveals mildly elevated glucose to 150 and glycohemoglobin in 7.5 mg/dL. Genetic testing revealed PRSS1 mutation. Patient was followed for several months and continued to have recurrent pancreatitis and nonnarcotic requiring abdominal pain. MRI had a low T1 signal, and secretin-enhanced MRCP revealed a mildly irregular main ductus pancreas with multiple side-branch dilations. Total pancreatectomy with autologous islet transplant was performed. Final pathology revealed inflammation, fibrosis, and atrophy consistent with CP.

Diagnosis: chronic autoimmune pancreatitis, imaging grade III, physiology stage D

Diagnosis case 4: definitive evidence. A 18-year-old female college freshman presents to emergency department with acute onset of abdominal pain, nausea, and vomiting. Amylase and lipase are both >3×ULN; liver function test (LFTs) are normal. Computed tomography imaging suggests focal inflammation and fullness of pancreas. MRI scan is suggestive of AIP with focal dilation of pancreatic tail in region of parenchymal inflammation. EUS confirms findings on cross-sectional imaging; there is no evidence for a mass. Periampullary biopsies and staining for IgG4 are negative. Serum IgG4 is normal. Fecal elastase >500 μg/g. Patient abdominal pain requiring narcotics to control, intractable to 5 weeks of steroids and 1 week hospitalization for pancreatic rest (nothing by mouth (NPO)). Repeat MRI and EUS confirm previous findings with persistent focal dilation of distal duct; fine needle aspiration (FNA) biopsy was nondiagnostic. Distal pancreatectomy recommended for intractable pain and concern of focal duct dilation. Pathology revealed ductentric lymphoplasmacytic infiltration suggestive of AIP; IgG4 staining is negative.

Diagnosis: chronic autoimmune pancreatitis, imaging grade IV, physiology stage A to emphasize salient features of the proposed diagnostic evaluation (Table 9).

It is our intent that this manuscript serve as a baseline “working document” that will be modified as new evidence becomes available and our knowledge of CP improves.

REFERENCES

References are available online at: http://links.lww.com/MPA/A335.