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Academic Pancreas Centers of Excellence: Guidance from a multidisciplinary chronic pancreatitis working group at *PancreasFest*

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Potential conflicts of interests related to this work

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Abstract

Chronic pancreatitis (CP) is a progressive inflammatory disease, which leads to loss of pancreatic function and other disease-related morbidities. A group of academic physicians and scientists developed comprehensive guidance statements regarding the management of CP that include its epidemiology, diagnosis, medical treatment, surgical treatment, and screening. The statements were developed through literature review, deliberation, and consensus opinion. These statements were ultimately used to develop a conceptual framework for the multidisciplinary management of chronic pancreatitis referred to as an academic pancreas center of excellence (APCOE).

Keywords

Chronic pancreatitis; Diagnosis; Treatment

Introduction

Chronic pancreatitis (CP) is a progressive inflammatory disease in which replacement of the pancreas by fibrosis results in end stage complications that include loss of acinar and islet cells [1]. Hence, it is important to develop a strategic approach to comprehensively address various management aspects of this disease. There are also variable patterns of disease progression; however, for the vast majority, the disease is characterized by substantial disease-related morbidity, including chronic abdominal pain, exocrine insufficiency, and/or endocrine insufficiency. Pain, when present, can be severe, impair mental and physical quality of life, lead to secondary substance abuse disorders, and frequent hospitalizations [2,3]. There is also a higher risk of pancreatic adenocarcinoma in patients with CP, further amplified by smoking, diabetes, and genetics [4]. Lastly, the all-cause mortality from CP is worse than age-matched controls [5,6]. Given the complexity of CP and its consequences to patients the diagnosis, treatment, and monitoring of complications requires a multidisciplinary approach.

Although guidelines have been published regarding the diagnosis and management of CP [7–10], there are no systematic guidelines to direct a multidisciplinary approach by centers to achieve a uniform degree of excellence in patient care. Thus, there is a need for guidance regarding how to improve patient care through adherence to best practices, as well as addressing research and educational needs.

A clinical center of excellence is a conceptual means of designating institutions that can provide an array of select services that maximize quality in patient care. In other areas of medicine such centers have been developed with the aim of treating a specific disease or group of diseases, such as cystic fibrosis, bariatric surgery, stroke, and breast care; many of these centers are ultimately endorsed and/or accredited by medical societies and foundations. Considering the disease burden associated with CP, which often requires multidisciplinary management, the National Pancreas Foundation (NPF) recently developed

criteria to designate “NPF Pancreatitis Centers”, which are recognized for their provision of services required to provide excellent patient care. However, recognizing large knowledge gaps in our understanding of CP and resultant management decisions a group of international investigators at *PancreasFest* set out to develop complimentary means of designating centers, herein referred to as an Academic Pancreas Centers of Excellence (APCOE) committed to excellence in not only patient care, but also research and education. We discuss the development of a series of guidance statements regarding the management of CP and propose key components of an APCOE, including: patient care, designated care personnel, standard ancillary services, research, training and education, hospital compliance, pancreatic function testing, and total pancreatectomy with islet auto transplantation (TPIAT).

Methods

Guideline focus and development process

PancreasFest is an annual conference attended by participants with an interest in pancreatology, including but not limited to, pancreatologists, endoscopists, radiologists, surgeons, scientists, geneticists, oncologists, and epidemiologists. At *PancreasFest* 2014, under the direction of the course directors (DLC, DCW), leaders of several academic pancreas centers met and selected areas of interest regarding CP for which statements were needed to provide comprehensive guidance to minimize variation in clinical practice, including: *epidemiology, diagnosis, medical treatment, surgical treatment, screening*, and *research and education*. Leaders were selected for each group from the list of participants.

Each sub-working group carried out literature reviews and sought input to identify key gaps in knowledge to develop discussion questions and corresponding guidance statements. Working groups held a series of web conferences to develop and refine guidance statements to answer these questions. At *PancreasFest* 2015 the discussion questions and guidance statements were presented to the group-at-large including a summary of the level of evidence and grade of recommendation. This process was similar to and guided by the experience from the guideline development regarding total pancreatectomy and islet autotransplantation in chronic pancreatitis, which was developed at *PancreasFest* 2012 [11].

Evidence review and grading

Each guidance statement and recommendation was graded according to the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) grid, the Surviving Sepsis Campaign report, and according to the Oxford Center for Evidence-Based Medicine (http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/), based on the level of evidence available (Table 1) [12,13].

Level of agreement

The discussion questions, guidance statements, and level of evidence and grade of recommendation were presented to the group of at-large voting delegates (n = 67). Participants submitted anonymous votes using options listed in Table 2.

Guidance statements

Epidemiology of chronic pancreatitis

Section leaders: Gregory A. Cote, MD, MS and Dhiraj Yadav, MD, MPH—

Question: Should there be a universal standard for collection and reporting of clinical information from patients with chronic pancreatitis?

Guidance statement 1.1. Standardization of clinical data obtained during evaluation and follow up of patients with suspected or proven chronic pancreatitis patients has several advantages. This will help to establish quality of care measures, determine how often such measures are fulfilled at individual centers and allow for comparison of care delivered and outcomes between centers.

Evidence level: 3b

Grade of Recommendation: B

Level of Agreement: A 72%; B 26%; C 0%; D 2%; E 0%

Discussion: Expert reviews and guidelines make recommendations on different aspects of care and follow up of patients [7–10,14–18]. Although natural history studies inform us of the presentation and course of chronic pancreatitis [19–22], providing information on the probability of outcome(s) tailored to individual patients is not currently possible. Unfortunately, there are no standardized measures for use in CP patients. As a result, the type and quality of care provided to patients at different centers remains unknown. Standardizing the collection and reporting of clinical information from patients will have several advantages. These data should include, but not be limited to, risk factor assessment, clinical symptoms, features of CP, resource utilization and quality of life assessment at different stages during the care of patients. The terminology used for the reporting of radiology, endoscopy and pathology reports should be standardized.

Question: How often should patients with chronic pancreatitis be evaluated?

Guidance statement 1.2. Patients with stable chronic pancreatitis should be evaluated at least yearly. The need for additional follow-up should be adjusted based upon the presence and severity of associated symptoms.

Evidence level: 2b

Grade of Recommendation: B

Level of Agreement: A 64%; B 27%; C 9%; D 0%; E 0%

Discussion: The age at symptom onset as well as development and/or performance of relevant conditions/procedures should be recorded. Follow-up may include visits in gastroenterology, hepatobiliary-pancreatic surgery, endocrinology, behavioral medicine, and/or pain medicine. At each follow-up encounter, the clinical history should include assessment for changes in pancreatitis-related symptoms or interval hospitalizations,

development of new symptoms particularly those that may suggest cancer, functional abnormalities (exocrine and/or endocrine insufficiency), morphological changes on imaging (if performed) and laboratory testing. In this context, any diagnostic or therapeutic intervention(s) performed during each follow-up period should be summarized, including the results and outcomes for each. There are inadequate data to make a universal recommendation regarding the frequency of follow-up imaging, which needs to be tailored to the individual patient.

Diagnosis of chronic pancreatitis

Section leaders: Sunil Sheth, MD; Vikesh Singh, MD, MSc—Question: What is the definition of chronic pancreatitis (CP)?

Guidance statement 2.1. CP is a progressive irreversible inflammatory disease where the pancreatic parenchyma is replaced by fibrous tissue leading to a loss of acinar and islet cells, usually in the setting of environmental or genetic risk factors, and typically characterized by the presence of pain and/or exocrine and/or endocrine insufficiency.

Evidence level: 5

Grade of Recommendation: D

Level of Agreement: A 67%; B 20%; C 4%; D 9%; E 0%

Discussion: Traditional definitions of CP relied on the presence of advanced, or end-stage features. Early features are non-specific, and overlap with other clinical problems [23]. To address this issue, an international collaboration of experts were asked by the International Association of Pancreatology and the European Pancreas Club (EPC) to develop a new consensus definition of CP. This initiative followed the development of the preceding definition and voting for the guidance statement, but the content remains consistent. The proposed mechanistic definition describes the essence and characteristics of classic CP[1]. The new definition defines the essence of CP as “a pathologic fibro-inflammatory 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 listed characteristics of established and advanced CP include, “pancreatic atrophy, fibrosis, pain syndromes, duct distortion and strictures, calcifications, pancreatic exocrine dysfunction, pancreatic endocrine dysfunction, and dysplasia.” The new definition was accepted by the EPC on July 6, 2016, and by the delegates to PancreasFest on July 28, 2016. A progressive model of disease, which was also endorsed, accompanies the mechanistic definition.

Question: How is chronic pancreatitis diagnosed?

Guidance statement 2.2. CP is a syndrome consisting of symptoms, structural, and/or functional abnormalities. The diagnosis of advanced CP is usually straightforward; however, the diagnosis of early, mild, non-calcific, or minimal change CP is challenging.

Evidence level: 5

Grade of Recommendation: D

Level of Agreement: A 71%; B 22%; C 4%; D 0%; E 2%

Discussion: Patients with advanced CP typically have at least two of the three following findings: 1) abdominal pain and/or acute pancreatitis; 2) structural changes of the gland on imaging, including calcifications and/or moderate to severe changes of the pancreatic duct based on the Cambridge classification [24]; and 3) exocrine and/or endocrine insufficiency. Structural changes of the pancreas can be diagnosed with standard abdominal imaging studies, including computed tomography (CT), magnetic resonance imaging (MRI), and plain radiograph in the setting of bulky calcifications [8]. The pancreatogram is often abnormal demonstrating dilation, beading, and irregularity of the pancreatic duct as well as the presence of ectatic side branches which are shortened and dilated. Stool tests may indicate fat malabsorption. In some patients, it may be necessary to exclude pancreatic cancer, cystic neoplasms, autoimmune pancreatitis, lymphoma, and pancreatic neuroendocrine tumors. Moreover, there are different clinical phenotypes in CP: patients can present with CP characterized by pancreatic insufficiency without pain (especially those with cystic fibrosis and “late onset” idiopathic pancreatitis). Although pancreatic gland atrophy is often seen on imaging, this has never been studied as an imaging feature of chronic pancreatitis in isolation of other features. Chronic calcific pancreatitis is typically found in patients with CP secondary to significant alcohol consumption or gene mutations, and some patients present early in their clinical course with abdominal pain and/or acute recurrent pancreatitis with minimal or normal imaging findings.

Recent American Pancreatic Association (APA) diagnostic guidelines classify evidence for the diagnosis of CP as definitive, probable, or insufficient evidence, in patients with abdominal pain suspected of having CP, and with exocrine/endocrine insufficiency, genetic risk factors, heavy alcohol or smoking history [8]. For several reasons, it is recommended that without sufficient evidence patients should not be labeled with a diagnosis of CP. The APA also recommends a diagnostic algorithm that proceeds from a noninvasive to a more invasive approach which maximizes the specificity in patients suspected of having CP.

Question: What are the challenges in the early diagnosis of chronic pancreatitis?

Guidance statement 2.3. The accurate diagnosis of CP in its early stages remains difficult for many reasons, including an inability to differentiate pancreatic versus non pancreatic chronic upper abdominal, the lack of consensus on the degree of histological changes needed to diagnose chronic pancreatitis, and the fact that advanced imaging (endoscopic ultrasonography (EUS) and secretin-stimulated magnetic resonance cholangiopancreatography (s-MRCP) and functional studies (endoscopic pancreatic function tests) can be abnormal in asymptomatic patients who are older, obese, smoke, and/or use alcohol.

Evidence level: 3b

Grade of Recommendation: B

Level of Agreement: A 71%; B 27%; C 2%; D 0%; E 0%

Discussion: The typical patient suspected of having early chronic pancreatitis presents with chronic upper abdominal pain, worse with eating, and in whom standard cross-sectional imaging is normal or show changes that may not be diagnostic of CP. Though there have been advances in our understanding of the nociceptive transmission by peripheral nerves to the central nervous systems and the alterations that occur leading to central sensitization, our ability to clinically differentiate pancreatic from non-pancreatic pain remains limited [25]. This is highlighted by the fact that pain does not correlate with histologic fibrosis [26] or even advanced imaging findings of CP[27]. Similarly, abnormalities are also seen on advanced imaging in those who are older, obese, smoke, and/or use alcohol, but without any clinically evident pancreatic disease [28–31].

A proportion of patients with presumed early chronic pancreatitis (also variably referred to as mild CP, minimal change CP, or noncalcific CP) do not have significant structural features such as calcifications or ductal changes. Also, some patients can be asymptomatic for long periods of time or indefinitely. For instance, in autopsy studies of chronic alcoholics, 50% had fibrosis in the pancreas, but only 10% had clinical CP [32]. Disease progression is also affected by genetic mutations as well as environmental toxins, such as ongoing tobacco and alcohol use [1]. Given the heterogeneous initiation, patchy distribution of disease, and variable progression, diagnosing early chronic pancreatitis in the absence of overt manifestations is difficult.

Question: What is the diagnostic strategy for making or excluding a diagnosis of early chronic pancreatitis?

Guidance statement 2.4. A combination of endoscopic pancreatic function testing (ePFT), s-MRCP, and EUS may be useful in the diagnosis of early CP among those patients with risk factor(s) for developing CP. The role of these expensive and nonspecific tests in patients without risk factors for CP is questionable at the present time.

Evidence level: 4

Grade of Recommendation: C

Level of Agreement: A 35%; B 39%; C 17%; D 9%; E 0%

Discussion: Chronic pancreatitis is often suspected in patients with characteristic upper abdominal pain, with slightly increased or normal serum pancreatic enzyme levels and normal CT and MRI, especially if they have risk factors such as smoking, alcohol, history of acute pancreatitis, and/or a family history of pancreatitis. There is no true “gold standard” for diagnosis, including histology, which can show overlapping histologic features in asymptomatic elderly patients, diabetics, smokers, and alcohol users [33–35]. Further, there is no agreement on the number of criteria to diagnose CP in early stages both for EUS and s-MRCP, which primarily provide measurements of fibrosis and inflammation, not specifically the clinical entity of CP.

In spite of these limitations, s-MRCP, ePFT, and EUS appear to be the best tests among available options, even though they are concordant in only 70–75% of patients [8]. This is likely because early CP is a patchy disease with variable structural and functional abnormalities which may progress at different rates in each patient. Hence, experts suggest that it may be best to combine a functional and structural test to increase both the sensitivity and specificity for diagnosing early CP, taking into account the pre-test probability for disease [1]. Thus, based on the available evidence, we suggest a multimodal approach using EUS, s-MRCP, and ePFT after stratifying patients into high (smoking, alcohol, history of acute pancreatitis and a family history of pancreatitis) and low risk groups for early CP based on their clinical history, and depending on the availability of combined EUS/ePFT testing. In low risk groups suspected of having CP, secretin function testing has shown promise in excluding chronic pancreatitis in one study, given its very high negative predictive value (97%) [36]. Future prospective studies are needed to validate this approach by correlating early abnormalities with the development of later stages of disease (such as calcifications, extensive fibrosis, diabetes, steatorrhea, weight loss, etc.) during longitudinal follow-up.

Medical management of chronic pancreatitis

Section leaders: Andres Gelrud, MD; Jamie Barkin, MD—Question: What specialty care services are needed for a multidisciplinary approach to chronic pancreatitis?

Guidance statement 3.1. The APCOE should include physicians within the following specialties for elective and urgent care: clinical pancreatologist (or gastroenterologist with interest in pancreatology), interventional endoscopy and radiology, and surgery with pancreatico-biliary expertise.

Evidence level: 5

Grade of Recommendation: D

Level of Agreement: A 89%; B 9%; C 2%; D 0%; E 0%

Guidance statement 3.2. The APCOE should have on-site or referral services in place for pain management, nutritionist, genetic counselor, endocrinology, social services, and psychologist.

Evidence level: 5

Grade of Recommendation: D

Level of Agreement: A 98%; B 2%; C 0%; D 0%; E 0%

Guidance statement 3.3. During the first visit, patients with chronic pancreatitis and untreatable pain should be referred to the pain clinic for management.

Evidence level: 2b

Grade of Recommendation: B

Level of Agreement: A 22%; B 22%; C 20%; D 29%; E 6%

Discussion: A multidisciplinary approach to pancreatitis patients is generally recommended, however there is lack of agreement regarding the timing of referral to a pain clinic for those with a chronic abdominal pain syndrome. Some prefer to involve pain specialists early in the patient-physician relationship, whereas others may elect to wait until patients have failed other interventions such as non-steroidal anti-inflammatory medications, antioxidant therapy, gabapentinoids, and/or weak opioids. Even in the absence of supporting evidence, there was a near unanimous agreement regarding the value of supporting clinical services. For example, involvement of psychology (or other forms of clinical support for chemical dependency) play a critical role in assisting patients with tobacco cessation and alcohol avoidance. Genetic counselors serve a valuable role in assisting with the evaluation of those with suspected hereditary pancreatitis, including counselling regarding the potential implications of a positive test result and provision of family counselling for patients of reproductive age. The creation and implementation of management protocols should be integrated across all practice locations including emergency department, and inpatient and outpatient settings to standardize and optimize care.

Question: What are the indications for endoscopic interventions?

Guidance statement 3.4. Strong indications for endoscopic retrograde cholangiopancreatography (ERCP) are biliary pancreatitis with rising bilirubin and dilated bile duct. Another indication is pancreatic duct stricture and/or stone with upstream dilation of the pancreatic duct.

Evidence level: 2b

Grade of Recommendation: B

Level of Agreement: A 43%; B 33%; C 22%; D 0%; E 2%

Guidance statement 3.5. At least two proficient gastroenterologists should be able to provide therapeutic endoscopy.

Evidence level: 5

Grade of Recommendation: D

Level of Agreement: A 56%; B 26%; C 15%; D 2%; E 0%

Guidance statement 3.6. Access to therapeutic ERCP and diagnostic and therapeutic EUS should be available.

Evidence level: 5

Grade of Recommendation: D

Level of Agreement: A 89%; B 9%; C 0%; D 0%; E 2%

Guidance statement 3.7. Endoscopic expertise on the treatment of transmural (gastric/duodenum) pseudocyst and/or walled off necrosis drainage should be available.

Evidence level: 1b

Grade of Recommendation: A

Level of Agreement: A 55%; B 38%; C 4%; D 2%; E 0%

Guidance statement 3.8. Technology for large pancreatic duct stone fragmentation should be available including extra corporeal shock wave lithotripsy (ESWL), per-oral pancreatoscopy guided laser lithotripsy (POP-LL), or electrohydraulic lithotripsy (EHL), but is not mandatory.

Evidence level: 3a

Grade of Recommendation: B

Level of Agreement: A 32%; B 49%; C 15%; D 6%; E 0%

Discussion: ERCP is one of the most technically demanding and high risk procedures performed by gastroenterologists. It requires a fully trained and experienced endoscopist to maximize success and minimize poor outcomes [37]. ERCP has evolved into a predominantly therapeutic procedure with well-defined indications [38]. Endoscopists performing ERCP should have fulfilled American Society for Gastrointestinal Endoscopy (ASGE) criteria for training and acquiring clinical privileges to assure high quality during ERCP.

Many studies have shown that success during ERCP and complication rates are related to volume of procedures. When complications do occur, early recognition and therapy is crucial. Consultation may be needed from hepatopancreaticobilary surgery and interventional radiology to optimize patient management. In contrast, though EUS is primarily used for diagnostic purposes, it also has important therapeutic applications. EUS is now commonly performed for drainage of pancreatic and peripancreatic fluid collections and to access the pancreatic duct. The recommendation for at least two therapeutic endoscopists is based on the practical need to ensure continued availability for management of urgent problems and complications. There is a learning curve to achieve technical and clinical success of both EUS and ERCP; however, there is substantial variability among trainees and a specific case volume does not ensure competency [39,40]. Similarly, complex therapeutic interventions with increased risks (such as transmural drainage of pancreatic pseudocysts) should likely only be performed by those with an exceptional endoscopic skillset and low complication rates. However, further study is needed to develop competency metrics that correlate with technical and clinical outcomes.

Patients with pancreas divisum and recurrent acute pancreatitis may benefit from ERCP and minor sphincterotomy particularly if the dorsal duct is dilated. Mutations in the CFTR and SPINK1 genes in patients with pancreas divisum have been associated with recurrent acute pancreatitis, suggesting a multifactorial origin of pancreatitis [41,42]. When large (≥10 mm)

pancreatic duct stones are present in a symptomatic patient, ESWL, POP-LL, and EHL may help to fracture stones and facilitate extraction with good long term pain relief [43,44]. However, surgery in this setting may provide more durable pain relief.

Question: What are the indications for total pancreatectomy with islet autotransplantation (TPIAT) in CP?

Guidance statement 3.9. The primary indication is to treat debilitating pain in patients with impaired quality of life due to CP in whom medical and/or endoscopic therapy has failed.

Evidence level: 2a

Grade of Recommendation: B

Level of Agreement: A 58%; B 29%; C 9%; D 4%; E 0%

Guidance statement 3.10. Optimal timing of TPIAT is determined by the severity, frequency, and duration of pain, narcotic requirements, impaired quality of life, residual islet function and age of the patient

Evidence level: 2a

Grade of Recommendation: B

Level of Agreement: A 55%; B 33%; C 7%; D 2%; E 2%

Discussion: The use of TPIAT for management of CP has been reviewed [11]. Patients with known genetic causes of CP (especially when associated with a pathogenic mutation of the PRSS1 gene) should be given special consideration for TPIAT because the disease is likely to progress and no genetic therapies are currently available [11]. Prior to surgery, the patient must be evaluated by the multidisciplinary transplant team and approved for surgery. The lifelong need for pancreatic enzyme replacement therapy and high likelihood of developing diabetes should be clearly explained and understood by the patient and family. The optimal timing is not well described and future studies are needed.

Question: What type of training program should be available in an APCOE?

Guidance statement 3.11. Clinical training in pancreatitis (inpatient and outpatient) must be available for either a gastroenterology fellow or fourth year dedicated fellow (not mandatory).

Evidence level: 5

Grade of Recommendation: D

Level of Agreement: A 51%; B 24%; C 13%; D 9%; E 2%

Guidance statement 3.12. More than one member of the pancreas team should be able to oversee the clinic.

Evidence level: 5

Grade of Recommendation: D

Level of Agreement: A 43%; B 20%; C 20%; D 16%; E 0%

Guidance statement 3.13. Clinical training in pancreatitis (inpatient and outpatient) should be available for a physician assistant, nurse practitioner, or research coordinator.

Evidence level: 5

Grade of Recommendation: D

Level of Agreement: A 43%; B 20%; C 20%; D 16%; E 0%

Discussion: Training to become a clinical pancreatologist requires understanding of the physiology and pathophysiology of the pancreas. Exposure to the inpatient and outpatient setting is important, because the management in these two clinical scenarios is very different. Ideally a gastroenterology fellow with an interest will join the APCOE early in his/her career. Trained support staff for clinical care and research protocols should be involved in the team.

Question: How should exocrine pancreatic insufficiency (EPI) be treated?

Guidance statement 3.14. Pancreatic enzyme replacement therapy (PERT) dosing is calculated by body weight. According to the Cystic Fibrosis Foundation patients who are over the age of 4 should take 500 to 2500 IU lipase per kilogram per meal.

Evidence level: 1b

Grade of Recommendation: A

Level of Agreement: A 42%; B 26%; C 22%; D 0%; E 10%

Guidance statement 3.15. PERT should be taken with meals (either in the beginning of the meal or in the middle and one at the end of the meal) and half the dose with snacks.

Evidence level: 1b

Grade of Recommendation: A

Level of Agreement: A 33%; B 33%; C 22%; D 8%; E 4%

Guidance statement 3.16. Once the diagnosis of EPI has been made vitamin supplementation should be performed, particularly fatsoluble vitamins.

Evidence level: 2b

Grade of Recommendation: B

Level of Agreement: A 49%; B 20%; C 20%; D 10%; E 0%

Discussion: EPI refers to the inadequate production or secretion of pancreatic enzymes to properly digest orally ingested nutrients. This results in several symptoms, which are mostly the consequence of fat maldigestion. Similarly, patients with EPI are at increased risk for developing fat-soluble vitamin deficiencies. For example, in a recent cross-sectional study, the estimated frequency of deficiencies in vitamin A, D, E, and K was 3, 53, 10, and 63%, respectively [45]. Since symptoms generally do not develop until later in the course of EPI, we recommend routine laboratory screening for these nutrients even in those without a clinical diagnosis of EPI. Generally, vitamin supplementation is only provided for those with deficient levels, but may be considered in all subjects diagnosed with EPI.

When PERT is recommended, the medication should be taken with food to optimize mixing with ingested nutrients. The dosing of PERT needs further investigation and consensus development. Even though several of these products contain an FDA-approved label (and foundation endorsement) for weight-based dosing, the rationale for this approach remains puzzling as these medications are not dependent on volume of distribution. The ideal approach would be to individualize dosing based on objective, serial measurement of exocrine function, which does not currently exist. In the absence of this marker, monitoring a response to symptoms, weight, and vitamin levels remains critical.

Surgical management of chronic pancreatitis

Section leader: Katherine Morgan, MD—Question: What is the role of a multidisciplinary team for the surgical management of CP?

Guidance statement 4.1. A multidisciplinary collaborative is an essential component of optimal surgical care of the patient with pancreatic disease. Multidisciplinary clinics allow specialists with varying expertise and perspective to work together to develop consensus recommendations.

Evidence Level: 3b

Grade of Recommendation: B

Level of Agreement: A 85%; B 15%; C 0%; D 0%; E 0%

Discussion: Optimal surgical care for chronic pancreatitis benefits from an organized multidisciplinary approach to patients. This comprehensive team includes the multiple medical specialties with an emphasis in pancreatology, including gastroenterology, pancreatobiliary surgery, pathology, interventional radiology, pain management, and behavioral health. Each of these disciplines offers an essential and unique component to the care of the pancreas patient, given the many modalities available to approach pancreatic diseases. Team care allows for best practice decision-making and can improve the quality of patient care [46]. For example, Pawlik and colleagues found that a multidisciplinary clinical team evaluation led to changes in therapeutic recommendations in 23.6% of pancreatic cancer patients [47]. Notably, in the current era, pancreas “surgery” is probably more accurately described as pancreas “intervention,” recognizing that many approaches (open surgery, laparoscopy, robotic surgery, endoscopy, and image-guided percutaneous

techniques) can be undertaken to achieve the same goal. Thus, a multidisciplinary approach is needed to weigh the various diagnostic and therapeutic options to optimize a patient's care. Most data regarding the impact of multidisciplinary care in pancreatic surgery has been focused on pancreatic cancer, so additional studies should be undertaken to more precisely measure the impact in chronic pancreatitis.

Question: What level of pancreatic surgical expertise is necessary to maintain good patient outcomes in the surgical management of CP?

Guidance statement 4.2. Pancreas centers of excellence should have pancreas specific surgical expertise, including a breadth and depth of experience with surgery of the pancreas. This experience can be measured objectively by surgical case volume. While the actual volume cutoff is controversial, available evidence suggests >11 resections per year as defining a high-volume pancreas surgery center.

Evidence Level: 2a

Grade of Recommendation: B

Level of Agreement: A 43%; B 25%; C 20%; D 5%; E 7%

Discussion: Pancreas specific expertise is essential to high quality surgical outcomes. Though direct perioperative outcomes measures are the preferred metrics for defining pancreas-specific expertise, these measures are challenging to track and direct correlation with patient-reported outcomes are lacking (see Guidance Statement 1.1). High institutional pancreas surgery volume, however, has consistently been demonstrated to correlate with improved outcomes, including decreased morbidity, length of stay, hospital cost, mortality, and long term survival [48–55]. However, there are limitations with the metric of case volume since there is still heterogeneity in outcomes even among individual high volume providers [56]. Thus, annual case volume >11 resections per year should be considered a helpful, but not definitive, surrogate marker for postoperative outcomes of pancreatic surgery; this should likely be considered as a minimum requirement for achieving good patient outcomes.

Question: What is the role of standardized patient care pathways for surgical management of CP?

Guidance statement 4.3. Standardized patient care pathways are an integral part of best surgical care of the patient with pancreatic disease.

Evidence Level: 3a

Grade of Recommendation: C

Level of Agreement: A 56%; B 33%; C 5%; D 7%; E 0%

Discussion: Standardized patient care pathways are essential for achieving the highest level of patient care. These evidence-guided pathways result in consistent care and improved

quality. Patient care pathways have been shown to dramatically enhance surgical outcomes, including decreased morbidity and improved efficiency [57–64]. A recent systematic review and meta-analysis of studies reporting outcomes after the implementation of enhanced recovery after pancreas surgery protocols suggested that enhanced recovery protocols shorten hospital length of stay and reduce morbidity, without increasing readmission rates or mortality [65].

Question: What is the role of measuring and analyzing perioperative outcomes in the surgical management of chronic pancreatitis?

Guidance statement 4.4. A pancreas center of excellence should participate in comprehensive perioperative outcomes data collection and analysis to ensure delivery of the highest quality surgical care and to allow for systematic quality improvement.

Evidence Level: 2b

Grade of Recommendation: B

Level of Agreement: A 84%; B 11%; C 5%; D 0%; E 0%

Discussion: Collection and analysis of surgical outcomes data has been shown to improve morbidity and mortality rates across many surgical disciplines. The National Surgical Quality Improvement Project (NSQIP), which was started in 1994, is now widely used with the support of the American College of Surgeons (ACS-NSQIP); this is an excellent example of using outcomes data assessment to improve the quality of patient care [66,67] ACS-NSQIP is a national program of surgical outcomes data collection, which provides risk adjusted data in a blind comparative format to participants, with the goal of measuring and optimizing the quality of surgical care. Interestingly, the ACS-NSQIP experience has shown that even data collection alone is associated with improved outcomes. Hall and colleagues reported on ACS-NSQIP data from 118 hospitals over 3 years, showing that 66% of participating hospitals improved risk adjusted mortality and 82% improved risk adjusted complication rates over the study period [68]. Subsequently a significant reduction in morbidity of gastrointestinal cancer surgery for participants of ACS-NSQIP over a 5 year study period was demonstrated [69]. Ideally, areas of poor performance identified with such comparative outcomes data incentivize quality improvement projects. For example, Ceppa and colleagues demonstrate the role of ACS-NSQIP reported superficial soft tissue infection rates in developing a successful improvement program for this morbidity after pancreas surgery [70].

Screening measures in chronic pancreatitis

Section leaders: Michelle Anderson, MD, MSc, Linda Lee, MD, Randall Brand, MD—Question: Should patients with CP undergo surveillance for EPI?

Guidance statement 5.1. At every office visit patients with CP should be asked for symptoms suggestive of EPI, including abdominal bloating, distention, frequent bowel movements (particularly after eating), weight loss, and the presence of steatorrhea (oily bowel movements, difficult to flush).

Evidence level: 1b

Grade of Recommendation: A

Level of Agreement: A 85%; B 11%; C 4%; D 0%; E 0%

Guidance statement 5.2. The final diagnosis of EPI is made by obtaining a fecal elastase in a semi-solid or solid bowel movement (if normal, EPI is ruled out) or 72 h stool collection with consumption of 100 gm fat/24 h. Other research tools are not widely available.

Evidence level: 2a

Grade of Recommendation: B

Level of Agreement: A 26%; B 46%; C 15%; D 4%; E92%

Guidance statement 5.3. Baseline serum levels of fat soluble vitamin and vitamin B12 should be obtained as part of the initial evaluation.

Evidence level: 2b

Grade of Recommendation: B

Level of Agreement: A 57%; B 24%; C 10%; D 4%; E 4%

Discussion: EPI most commonly occurs as a late stage result of CP, but also commonly occurs following total or partial pancreatectomy. Clinical symptoms of mild EPI are non-specific, including abdominal bloating and flatulence, whereas symptoms of severe EPI include steatorrhea and unintentional weight loss. There is no consensus regarding the preferred means for diagnosis of EPI, due to the lack of an accurate and convenient test [71]. Although fecal elastase-1 is often utilized due to the ability to perform the test on a single stool sample, the accuracy for diagnosis of mild EPI is only fair [72]. In contrast, determination of fecal fat from a 72 h stool collection is highly accurate, but inconvenient. There are many challenges to overcome regarding the diagnosis of EPI, and an attempt to reach a consensus regarding the preferred diagnostic strategy was not pursued by this group [71]. Nevertheless, a high index of suspicion should be maintained for EPI in patients with CP due to the high prevalence of this complication. If the pretest probability is high, a diagnostic trial with PERT may also be an option.

PERT is effective for decreasing fat malabsorption and has been shown in randomized, placebo-controlled trials to improve abdominal pain, improve stool consistency, and decrease stool frequency in patients with chronic pancreatitis [73,74]. Moreover, studies have shown that lower BMI is associated with lower quality of life in patients with chronic pancreatitis [75]. Based on these findings surveillance for EPI, and appropriate treatment, is recommended.

Question: Should CP patients be assessed for development of endocrine insufficiency (i.e., type 3c diabetes mellitus or pancreatogenic diabetes)?

Guidance statement 5.4. Patients with CP should be screened for development of diabetes.

Evidence Level: 2b

Grade of Recommendation: B

Level of Agreement: A 87%; B 8%; C 2%; D 2%; E 0%

Discussion: The epidemiology of type 3c diabetes mellitus (T3cDM) is difficult to accurately determine in the absence of validated diagnostic criteria; however, it is estimated approximately 4–5% of all diabetic subjects have T3cDM [76]. In one study CP was the most common etiology of T3cDM, accounting for 75% of cases [77]. Additionally, in those with CP the prevalence of diabetes ranges from 70 to 90%, depending on the severity and duration of disease [78,79]. Considering the exceptionally high prevalence of diabetes in those with CP, screening for diabetes is highly recommended, and is further reviewed elsewhere [18] [18].

Question: Should CP patients be screened for nutritional deficiencies and the development of osteopenia and osteoporosis?

Guidance statement 5.5. Patients with CP should be screened for nutritional deficiencies in fat soluble vitamins, minerals and trace elements on at least an annual basis and undergo a baseline bone mineral density (BMD) testing with subsequent monitoring and treatment based on assessment of fracture risk.

Evidence Level: 2a

Grade of Recommendation: B

Level of Agreement: A 65%; B 19%; C 13%; D 2%; E 2%

Discussion: The exocrine function of the pancreas is necessary for adequate absorption of the fat-soluble vitamins and as discussed above the prevalence of deficiencies is high, so it is advisable to regularly monitor these vitamin levels. Although the risk is less well characterized, it is also reasonable to consider concurrent evaluation for other vitamin (e.g., B12) and mineral or trace element deficiencies [80]. In patients with a history of previous pancreatic resection, additional tests may be needed such as copper and zinc levels, as these are absorbed almost exclusively in the duodenum.

The prevalence of CP-associated osteopathy (which includes osteopenia and osteoporosis) is approximately 65% [81]. Similarly, the risk of low-trauma fractures is increased in patients with CP[82, 83]. Osteopathy in chronic pancreatitis is multifactorial due to shared risk factors (e.g., vitamin D deficiency, cigarette smoking, female gender and alcohol use), as well as chronic inflammation. Despite the absence of formal societal endorsement, screening for osteopathy can be justified as the risk for decreased bone strength is higher than in other gastrointestinal diseases for which screening is already supported (e.g., celiac disease, inflammatory bowel disease, cholestatic liver disease, etc.). The most appropriate screening

interval is uncertain, but can likely be modified based on the collective assessment of risk, including the baseline screening results.

Question: Should patients with CP undergo screening for pancreatic cancer?

Guidance statement 5.6. There is insufficient data to recommend routine pancreatic cancer screening for patients with chronic pancreatitis.

Evidence Level: 2b

Grade of Recommendation: B

Level of Agreement: A 65%; B 18%; C 10%; D 4%; E 2%

Guidance statement 5.7. Clinicians should maintain a high index of suspicion for pancreatic cancer in patients with CP who develop additional risk factors (i.e., new onset diabetes with weight loss or advanced age) or a symptom complex consistent with pancreatic cancer (i.e., painless jaundice, weight loss, or abdominal pain radiating to the back).

Evidence Level: 2b

Grade of Recommendation: B

Level of Agreement: A 85%; B 13%; C 0%; D 2%; E 0%

Discussion: The risk of pancreatic cancer is increased in patients with CP, even after patients who develop pancreatic cancer within two years of CP diagnosis are excluded from analysis (to limit lead time biases from cases of delayed diagnosis) [84–86]. Though there is an increased risk of pancreatic cancer in patients with chronic pancreatitis (life-time risk of approximately 4%), there are no survival data from a controlled trial to support routine screening in this population [85,87]. Even in patients with forms of CP (i.e., hereditary (PRSS1) pancreatitis and tropical pancreatitis associated with a very high risk of pancreatic cancer (up to 40% by age 70) a survival benefit from screening has not been demonstrated [88]. Accordingly, no major societies currently recommend pancreatic cancer screening.

The development of pancreatic cancer screening, in general, has been hampered by several issues, all of which impact sensitivity and specificity of potential approaches. The screening utility of cross sectional and endoscopic imaging modalities can be limited in the setting of chronic pancreatitis because of pancreatic inflammation and scarring. Similarly, inflammation can limit the utility of cytologic and pathologic evaluation of pancreas tissue. Although many have been explored, none have been prospectively validated [89]. Though CA19-9 is often a useful clinical marker for following treatment response in pancreatic cancer, it lacks the sensitivity and specificity to be a good screening tool; CA19-9 may be normal in patients with early pancreatic cancer and can be elevated by benign intra-abdominal processes such as cholangitis that may present with symptoms similar to pancreatic cancer. Finally, the optimal initiation of pancreatic cancer screening, frequency, and duration is unknown and there is incomplete understanding of pancreatic carcinogenesis to direct clinical decisions.

Given the inherent challenges in pancreatic cancer screening, particularly for patients with chronic pancreatitis, novel screening tests (i.e. molecular testing, circulating DNA/RNA etc.) and approaches (i.e. pancreatic juice, urine, stool etc.) should continue to be evaluated [90,91]. A high index of suspicion should be maintained for pancreatic cancer for patients with chronic pancreatitis who develop new onset diabetes, unexplained weight loss, or new exocrine pancreatic insufficiency [92–95]. Standard diagnostic testing protocols should be followed in these situations, which may include endoscopic evaluation, cross-sectional imaging, and serum blood tests. Ongoing efforts to further study the relationship between CP and pancreatic cancer include the CAPS5 study and the NIH-funded Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer (CPDPC) [96].

Research recommendations

Section leaders: Fred Gorelick, MD, Stephen Pandol, MD

The role of education and clinical translation research was discussed within the context of pancreatic diseases in general with a focus on identifying specific needs related to acute recurrent (AP) and chronic pancreatitis (CP). The overriding goals in this area are to conduct and disseminate patient-centered research and develop education programs regarding current management and other advancements in the field. In addition to structured curricula for trainees regarding the evaluation and management of pancreatic disorders, there is a need to provide training and mentoring in the conduct of research. This includes study design, informed consent, transparency and elimination of bias, and statistical analysis. Areas of potential research related to CP were identified by the guideline coauthors and *Pancreas Fest* participants. These included additional research into the epidemiology, diagnosis, mechanisms of disease and treatment related to acute recurrent and chronic pancreatitis and their potential complications such as diabetes (type 3c) and cancer. Furthermore, there are a few guidance statements (2.4, 3.4, and 3.8) in which the agreement was not high and the level of evidence was low; these areas particularly warrant additional investigation, and are incorporated below:

Subtheme 1: Epidemiology

1. Continue to pursue additional understanding of the roles of genetic and lifestyle effects on the development of acute recurrent and chronic pancreatitis, particularly for those with presumed “idiopathic” CP.
2. Further characterize the prevalence and risk of type 3c diabetes and pancreatic cancer-related to pancreatitis.

Subtheme 2: Diagnosis

1. Identify and validate novel biomarkers and imaging features to facilitate the early diagnosis and personalized treatment of recurring pancreatitis and CP.
2. Further define unique histopathologic changes observed in CP and contrast with other causes of pancreatic fibrosis, including diabetic exocrine pancreatopathy.
3. Develop a testing strategy to distinguish type 3c from type 2 diabetes mellitus.

4. Develop an accurate and convenient test to diagnose and monitor effectiveness of therapy for exocrine pancreatic insufficiency (EPI).
5. Further characterize risk factors for the development of metabolic bone disease and pancreatic cancer in CP to identify a subset of patients who may benefit from more intensive screening.

Subtheme 3: Medical treatment

1. Develop quality indicators for the management of patients with chronic pancreatitis and use these to measure outcomes in patients with chronic pancreatitis, including quality of life and life expectancy.
2. Examine new interventions for CP-related pain, including pharmacologic and non-pharmacologic therapies such as cognitive behavioral therapy.
3. Test safety and efficacy of therapeutic strategies for type 3c diabetes.
4. Develop therapeutics for the prevention and treatment of chronic pancreatitis with a focus on quality of life and preventing progress to CP in individuals with acute recurrent pancreatitis.
5. Evaluate the effectiveness of therapeutic strategies to prevent the development and/or progression of metabolic bone disease in CP.
6. Develop clinical trial methods with outcome measures for testing interventions.
7. Perform clinical trials to further assess indications for endoscopic therapy, interventions for pancreatic duct stones, and promising pharmaceutical and nutritional interventions.

Subtheme 4: Surgical treatment

1. Optimize clinical care pathways for management of patients following pancreatic resection to decrease post-operative complications and length of stay.
2. Identify accurate methods to predict the analgesic response to currently utilized therapies, including TPIAT.

Subtheme 5: Screening

1. Develop an accurate and convenient test to diagnose and monitor effectiveness of therapy for EPI.
2. Further characterize risk factors for the development of metabolic bone disease and pancreatic cancer in CP to identify a subset of patients who may benefit from more intensive screening.

Criteria for Academic Pancreas Centers of Excellence for chronic pancreatitis

The National Pancreas Foundation (NPF) is a patient advocacy group founded in 1997, with a mission to provide hope for those suffering from pancreatitis and pancreatic cancer

through funding research, advocating for new and better therapeutics, and providing support and education for patients, caregivers, and health care professionals. Through an iterative process involving members of the Foundation, patient advocates, and invited physician content experts, criteria for designation as NPF Centers were developed (supplemental file). One of the key objectives for recognizing these institutions is to assist patients with identifying providers capable of providing multidisciplinary, patient-centered care. These criteria focus on the availability of onsite personnel, expertise, and services, or established referral patterns to provide patients with appropriate access to appropriate subspecialty care for the management of pancreatitis (acute and chronic), and aim to suggest standards related to patient care.

The concept and criteria for NPF Pancreatitis Centers was widely accepted by participants at *PancreasFest* 2015. Subsequently, *PancreasFest* working groups set out to develop a complementary designation to recognize APCOE's for chronic pancreatitis. In addition to providing excellence in patient care, APCOE's represent institutions emphasizing research, education, and training. Thus, the goal of the APCOE framework is to complement the ideals of the NPF Centers by providing trainee education and expanding our scientific knowledge related to pancreatic disorders to better inform best practices. These criteria (Table 3) were developed following presentation and review of the preceding guidance statements. Accordingly, they are guided by both available evidence and expert opinion. Criteria are classified as either required or preferred depending on the strength of evidence to support the statement and/or perceived importance to the mission of the APCOE.

Summary

Chronic pancreatitis is a condition associated with substantial disease-related morbidity, which requires a multidisciplinary approach. Institutions with specialized services are the best suited to provide optimal patient care, trainee education, and research. Based on literature review and expert consensus we have outlined a series of guidance statements regarding the management of CP, and have proposed a set of criteria to recognize institutions equipped to not only provide high quality patient care, but also improve best practices by addressing existing knowledge gaps through education and research.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ACS- NSQIP	American College of Surgeons-National surgical quality improvement project
APA	American Pancreatic Association
APCOE	Academic Pancreas Centers of Excellence
ASGE	American Society for Gastrointestinal Endoscopy
CP	chronic pancreatitis
CT	computed tomography
EHL	electrohydraulic lithotripsy
EPC	European Pancreas Club
ePFT	endoscopic pancreatic function testing
EPI	exocrine pancreatic insufficiency
ERCP	Endoscopic retrograde cholangiopancreatography
ESWL	Extra corporeal shock wave lithotripsy
EUS	Endoscopic ultrasonography
MRCP	Magnetic resonance cholangiopancreatography
MRI	Magnetic resonance imaging
NPF	National Pancreas Foundation
NSQIP	National surgical quality improvement project
PDAC	pancreatic ductal adenocarcinoma
PERT	pancreatic enzyme replacement therapy
POP-LL	Pancreatoscopy guided laser lithotripsy
s-MRCP	Secretin-magnetic resonance cholangiopancreatography
TPIAT	Total pancreatectomy and islet autotransplantation

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.pan.2017.02.015.

Table 1

Description of study features used to formulate the level of evidence of grade of recommendation.

Grade of recommendation	Level of evidence	Type of study
A	1a	Systematic review of (homogenous) RCTs
	1b	Individual RCTs (with narrow confidence intervals)
B	2a	Systematic review of (homogenous) cohort studies of “exposed” and “unexposed” subjects
	2b	Individual cohort study/low-quality RCTs
	3a	Systematic review of (homogenous) case-control studies
	3b	Individual case-control studies
C	4	Case series, low-quality cohort or case-control studies
D	5	Expert opinions based on non-systematic reviews of results or mechanistic studies

RCT, randomized controlled trial.

Table 2

The following voting options (A-E) were used to assess the level of support and agreement for proposed guidance statements.

Voting option	Level of support
A	Strongly positive
B	Weakly positive
C	Uncertain or equivocal
D	Weakly negative
E	Strongly negative

Table 3

Required criteria for to be designated as an Academic Pancreas Center of Excellence for Chronic Pancreatitis. Criteria regarding designated core personnel and hospital compliance reflect some qualifications that are specific to the United States, so equivalent requirements should be considered in other countries.

	Required criteria	Preferred criteria
Patient care	Commitment to excellence illustrated by designation as an NPF center	
Designated core personnel:		
Program director	Board certified and active membership in their respective specialty's national professional society	
Gastroenterology	Board certified with a clinical interest in the medical treatment of chronic pancreatitis (this may be the same individual as the program director and advanced endoscopist)	
Advanced Endo	≥2 endoscopists experienced in diagnostic and therapeutic EUS/ERCP	Ability to safely perform endoscopic therapy for peripancreatic fluid collections (including pseudocysts)
Radiology	Abdominal radiologist with expertise in CT and MRI/MRCP studies	Abdominal radiologist with expertise in secretin- stimulated MRCP studies
Pathology	≥2 pathologists with expertise in interpreting FNA and resected pancreatic specimens	
Surgery	• Center is considered a surgical referral center for pancreaticobiliary surgery • Participation in the national ACS NSQIP registry	Designated pancreaticobiliary surgeons perform ≥ 12 pancreatectomies per year
Research	Participation in single or multicenter clinical trials related to pancreatic disorders	IRB-approved biorepository protocol OR collaboration in a multicenter biorepository
Trainee Education	The following accredited fellowship program is required: • Gastroenterology and Hepatology	The following programs are preferred: • Advanced endoscopy • Medical pancreatology • Pancreaticobiliary surgery (or surgical oncology) • GI pathology • Abdominal imaging
Hospital compliance	Hospital is JCAHO-accredited, has an electronic medical record system, and infrastructure in place for monitoring of patient safety and quality related to endoscopy and surgery (e.g., GIQUIC, ASGE EURP, NSQIP)	Hospital has a CMS-compliant active physician quality reporting system (PQRS).
Standard ancillary services:		
Nutrition support	Resources, support staff, and access needed to provide and monitor home parenteral nutrition (i.e., TPN)	≥1 dedicated GI dietician
Pain control and anesthesia	Access to either an on-site or established referral pattern with a local pain management center	
Chemical dependency (tobacco/alcohol)	Access to either an on-site or an established referral pattern for management of chemical dependency	
Psychosocial support	Access to either on-site or an established referral pattern for a psychosocial support	

	Required criteria	Preferred criteria
Pancreas function testing (endocrine and exocrine)	• Ability to test for endocrine dysfunction, including oral glucose tolerance testing • Ability to perform indirect pancreatic function testing, including FE-1 or quantitative fecal fat analysis	Ability to perform direct pancreatic function testing (as indicated for evaluation of suspected early chronic pancreatitis).
Total pancreatectomy with islet autotransplantation (TPIAT)		• Access to either an on-site program or established referral pattern for patients with an appropriate indication • Ability to perform preoperative psychologic and chemical dependency evaluations