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International Consensus Statements on Early Chronic Pancreatitis.:

Recommendations from the Working Group for the International Consensus Guidelines for Chronic Pancreatitis in collaboration with the International Association of Pancreatology, American Pancreatic Association, Japan Pancreas Society, PancreasFest working group and European Pancreatic Club

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Abstract

Background: Chronic pancreatitis (CP) is a progressive inflammatory disorder currently diagnosed by morphologic features. In contrast, an accurate diagnosis of Early CP is not possible using imaging criteria alone. If this were possible and early treatment instituted, the later, irreversible features and complications of CP could possibly be prevented.

Method: An international working group supported by four major pancreas societies (IAP, APA, JPS, and EPC) and a *PancreasFest* working group sought to develop a consensus definition and diagnostic criteria for Early CP. Ten statements (S1–10) concerning Early CP were used to gauge consensus on the Early CP concept using anonymous voting with a 9 point Likert scale. Consensus required an alpha ≥0.80.

Results: No consensus statement could be developed for a definition of Early-CP or diagnostic criteria. There was consensus on 5 statements: (S2) The word “Early” in early chronic pancreatitis is used to describe disease state, not disease duration. (S4) Early CP defines a stage of CP with preserved pancreatic function and potentially reversible features. (S8) Genetic variants are important risk factors for Early CP and can add specificity to the likely etiology, but they are neither necessary nor sufficient to make a diagnosis. (S9) Environmental risk factors can provide evidence to support the diagnosis of Early CP, but are neither necessary nor sufficient to make a diagnosis. (S10) The differential diagnosis for Early CP includes other disorders with morphological and functional features that overlap with CP.

Conclusions: Morphology based diagnosis of Early CP is not possible without additional information. New approaches to the accurate diagnosis of Early CP will require a mechanistic definition that considers risk factors, biomarkers, clinical context and new models of disease. Such a definition will require prospective validation.

Introduction.

Chronic pancreatitis (CP) is one of the most difficult medical disorders to diagnose early and treat effectively. Advanced or End-stage CP is a well-described syndrome consisting of structural features of fibrosis, duct distortion, calcifications and/or atrophy, along with variable dysfunctional features of severe chronic pain, maldigestion and diabetes mellitus, and a long-term risk of pancreatic cancer. Patients with End-Stage CP typically struggle with pain relief, stigmatization, unemployment, and depression and often have among the worst quality of life measures for any chronic disease (1–3).

Tremendous effort and resources continue to be directed towards patients with end-stage disease. To avoid late stages complications and to improve clinical outcomes, diagnosis and treatment are essential at an early stage before CP becomes established and irreversible (4). Thus, it is important that increased efforts are directed towards early detection and targeted therapy in the hope of mitigating disease progression and improving the quality of life in a cost-effective, precision medicine approach (5).

The challenge in clinical care of patients with syndromes such as CP is that a “definitive diagnosis” is often only possible too late in the disease course to initiate treatments that might limit progression and/or minimize complications (4). Furthermore, between the onset

of various nonspecific signs and symptoms and the definitive diagnosis of CP by morphologic criteria, the patient often suffers from years of pain and distress while undergoing frequent diagnostic testing, such as in hereditary pancreatitis with an average delay of 9–10 years between symptom onset and a diagnosis (6, 7). In patients with atypical presentation and/or limited fibrosis (e.g. Cambridge score of <3 and/or not meeting Rosemont Criteria on EUS (8)) the diagnosis may be further delayed or missed altogether. Other consequences of delaying a definitive diagnosis include withholding effective treatments and/or giving inappropriate treatments (9).

A better understanding of the development, progression and treatment of CP is required. With that in mind, international experts have sought consensus on definitions, features and biomarkers related to the stages of CP. First, a mechanistic definition of CP was developed to better structure the features, interactions and stages of CP, and this definition was adopted by the major international pancreas organizations (10). A mechanism-based approach to assessment and management of pancreatic pain was published in 2017, taking into consideration the multidimensional nature of clinical presentation and variable response to specific therapies (11). Guidelines for the Diagnostic Cross Sectional Imaging and Severity Scoring of Chronic Pancreatitis have also been developed (submitted). But one of the most challenging areas for developing consensus is in Early CP because a definitive diagnosis of CP is impossible using the widely accepted imaging criteria (12). However, it may be possible to make a diagnosis of Early CP, in some cases, when CP is framed using the recently endorsed mechanistic definition and progression model (10). The aim was to determine whether consensus could be achieved for the definition and diagnostic criteria for Early CP and to highlight areas for further basic, translational and clinical research.

Historical definitions of Chronic Pancreatitis

Historically, the diagnosis of the CP syndrome was based on the triad of steatorrhea, pancreatic calcifications on abdominal X-ray and diabetes mellitus – evidence of end-stage disease. Early attempts to systematically define CP by morphologic, functional and clinical criteria occurred between 1963 and 1988 with three "*Marseille*" conferences (13–15). These conferences were fundamental in defining the characteristics of CP, but were relatively limited at the that time because of limited understanding of the complex risk factors for CP, particularly genetic, lack of sensitive imaging techniques and inadequate biomarkers of disease activity and progression. As a result the focus was necessarily on advanced CP with gross morphological features (16).

Significant improvements in abdominal imaging in the 1980s with computed tomography (CT), magnetic resonance imaging (MRI) and endoscopic retrograde cholangiopancreatography (ERCP) allowed more accurate assessments of morphologic changes, including the earlier stages of CP. An *International Workshop* held in Cambridge, England in March 1983 advanced the field with a working definition of CP based on morphology of the pancreas by ERCP imaging features, and an image-based severity scale (Cambridge Score) (12). The committee also recognized the limitations of imaging in making an early diagnosis. The conference report noted that the delegates "discussed the need for a grouping intermediate between acute and chronic pancreatitis, perhaps only as a

‘holding grade’ before final classification. This concept was eventually rejected, it being assumed that most clinicians would naturally use the term ‘probable chronic pancreatitis’ where necessary.” (12)

‘Early’ Chronic Pancreatitis.

The term “early-stage ACP” was used by Ammann, Heitz and Klöppel (17) to define a clinical stage linking alcoholic AP (AAP) and alcoholic CP (ACP). They argued that the diagnosis ‘early-stage ACP’ must be confirmed by criteria independent from histology, such as “long-term follow-up that eventually revealed the typical clinical features of CP” (17). Since Early-stage ACP could not be diagnosed with available clinical tests, the delegates to the 1996 Zürich Workshop used the term “Probable ACP” to describe the early phases of CP, typically lasting at least 5 years before “Definite ACP” could be diagnosed using morphologic features of End-stage CP. Thus, they defined a clinically important early stage that, at the time, could only be diagnosed in retrospect.

The majority of subsequent classification systems and consensus guidelines follow the Cambridge and Zürich Workshop recommendations of using morphologic criteria and applying the term “Probable CP” for cases with a high likelihood of CP but which do not meet imaging criteria of definite CP (18–21). For example, *The M-ANNHEIM* classification system follows the Zürich definitions, except for altering the criteria for “probable ACP” to “Borderline CP” for patients with “typical symptoms of chronic pancreatitis (i.e., recurrent episodes of acute pancreatitis) or with a first episode of acute pancreatitis who present without any morphological damage visible by means of pancreatic imaging techniques or detectable functional insufficiency suggestive of chronic pancreatitis” (22). The *American Pancreatic Association (APA) Practice Guidelines in Chronic Pancreatitis* (9) provided no definition for CP, but suggested classification of patients as “Definitive”, “Probable”, and “Insufficient” based on imaging studies or histology. The authors also recommended that patients in early stages should not be classified as having CP until definitive diagnostic features are evident (9). Most recently the *United European Gastroenterology* published guidelines for the diagnosis of CP (23), following the German S3 guidelines (18, 19) stating that the diagnosis of CP should be based on imaging modalities, but emphasized that imaging should be performed in *symptomatic* patients presenting with *indicators* suggestive of pancreatic disease. This reflects the Marseille approach where the diagnosis of CP is based on morphologic, functional and clinical criteria, but still with a focus on advanced disease.

In summary, these approaches recognized the existence of an early stage in progression of CP, but also recognized that the signs and symptoms of early disease are nonspecific, that progression is uncertain using the imaging approach to CP (8, 12) and that the diagnostic criteria required for a definitive diagnosis of CP using imaging techniques alone are not met. However, “Probable CP” (here used interchangeable with “Borderline CP”) is not a diagnosis, but rather a “placeholder” state, for those in whom CP high on the differential diagnosis list and is considered highly likely. The term “Possible CP” means that that CP ranks lower in the differential diagnosis list than other more likely diseases.

The *Japan Pancreas Society* (JPS) was the first major body to provide criteria for the diagnosis of Early CP (4). The 2009 revision of the diagnostic criteria for CP used the terms, “Definite CP”, “Probable CP”, and “Early CP” to classify pancreatic disease patients (4). The JPS “Definite CP” and “Probable CP” diagnosis are based on imaging criteria for “Advanced CP Findings” and “Probable CP Findings”, respectively (Figure 1). Subjects with imaging findings of Probable CP, but who *also* have two or more of the first three JPS functional/clinical findings (Table 1) are diagnosed with “Definite CP”. The JPS definition of “Early-CP” requires that cases do not qualify for a “definite” or “probable” diagnosis, that they satisfy two or more of the 4 functional/clinical criteria (including persistent drinking history of >80 g/day), and demonstrate appropriate imaging findings (4). These imaging criteria are based on EUS and/or ERCP examination. The definition of “Possible CP” requires that the patient meet the functional/clinical criteria, but do not meet imaging criteria (4, 24).

While the JPS approach provides a potentially useful definition of Early CP, it has not been accepted internationally. This might be because of two limitations: that the imaging criteria have low specificity for Early CP and that continued alcohol use is a requirement. To make progress towards a definition and diagnostic criteria for Early CP, these limitations need to be overcome and a new paradigm introduced.

Mechanistic Definition of CP.

A new mechanistic definition of CP was proposed to define the mechanism of disease and the typical characteristics of established disease (10). In the mechanistic definition, “Chronic pancreatitis is 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.” and “Common features of established and advanced CP include pancreatic atrophy, fibrosis, pain syndromes, duct distortion and strictures, calcifications, pancreatic exocrine dysfunction, pancreatic endocrine dysfunction and dysplasia.” Thus, the *Mechanistic Definition* does not require imaging features to define the disease.

Reliance on imaging as an essential requirement for the diagnosis of CP hinders the possibility of making early and definitive diagnoses of Early-CP. Initially, the diagnosis was hampered by limited sensitivity – but with improvements in imaging technology, the specificity of minor morphologic changes becomes the major challenge (25). Furthermore, current imaging techniques do not allow for the assessment or measure of most risk factors, degree of organ function, disease mechanism or disease activity.

The diagnosis of Early-CP requires a change in the way the CP disease is understood and managed. The mechanistic definition of CP (10) introduces a different framework for understanding and managing CP within the emerging concepts of precision medicine (5). Chronic pancreatitis is viewed as a complex disorder arising in high-risk subjects and progressing to end stage disease over time. More specifically, acquired diseases such as CP are more likely to develop in patients with one or more underlying molecular disorders, such as pathogenic *PRSS1, SPINK1, CFTR, CTRC, CEL and CLDN2* genetic variants within a stress-provoking environmental context (26–30) and in a clinical context such as RAP. The

new definition is built on a progressive model of CP beginning with an asymptomatic "At Risk" stage and progressing over time, in some individuals, to "End-Stage CP". This approach is *inclusive* of any susceptibility or modifying factors causing dysfunction of the normal process of *Injury* → *Inflammation* → *Resolution* → *Regeneration* originating in cells of the exocrine pancreas that ultimately lead to the characteristic pathological features of CP. The mechanistic definition also *excludes* disorders that cause pathology in the pancreas by different mechanisms, such as extrinsic duct obstruction, fibrosis from the desmoplastic reactions in pancreatic cancer or the pancreatopathy of long-standing diabetes mellitus and other disorders (25). Since the mechanistic definition of CP defines the process leading to the end-stage features of true CP, the earlier detection of this process has the potential to provide new diagnostic criteria for Early CP, including consideration of patients who are symptomatic but do not meet traditional imaging criteria for CP. Implementation of this mechanistic definition in clinical practice could prove beneficial in better defining and managing patients who are symptomatic of pancreatic disease, but in whom imaging results are non-specific or inconclusive for CP.

Goals and Objectives of an International Consensus Working Group on Early CP

Chronic pancreatitis is recognized as a heterogeneous syndrome that typically progresses from acute, recurrent and/or continuous inflammation of the pancreas to destructive and irreversible end-stage disease (10). Because of the complexity of CP and the differences between countries and populations, it is important that an advance in the understanding of this disease draws on international experience and expertise. This challenge is particularly relevant to the definition and diagnosis of Early CP where it is necessary to consider new ways to frame the disease, including the precision medicine paradigm that allows multiple interacting factors to be considered in parallel and sequence (5).

An international effort, including sixteen working groups was organized and commissioned to develop international consensus guidelines for the understanding and management of chronic pancreatitis in collaboration with the International Association of Pancreatology (IAP), American Pancreatic Association (APA), JPS and the European Pancreatic Club (EPC). The sub-group on Early CP (Chair; DCW) encompassing experts from the four major pancreas societies (IAP, APA, JPS, and EPC) and a *PancreasFest* working group.

Goals included:

1. To identify and invite a working group of international experts on the methods and criteria of the diagnosis of chronic pancreatitis.
2. To review the existing literature and emerging technologies related to Early CP
3. To hold an international consensus conference on Early CP that would be cosponsored by the IAP.
4. To develop an international consensus definition of Early CP.
5. To discuss and potentially develop consensus guidelines on the diagnosis of Early CP.

The first three goals were achieved. The last two goals were not achieved, but significant progress was made in defining the issues surrounding Early CP, and outlining the needs for future research.

Methods

The first approach to developing an international consensus on the definition of CP was a "consensus of consensus guidelines" promoted by the organizers of the combined EPC / IAP Meeting in Southampton, UK in June 2014. The outcome of this meeting was a draft Mechanistic Definition of CP (10) as described earlier. This was presented and accepted by voting members of the respective organizations during special sessions of the *European Pancreas Club* in Liverpool, UK (July 9, 2016), *PancreasFest 2016* in Pittsburgh, PA, USA (July 27, 2016) and the combined international Association of Pancreatology (IAP), *Japan Pancreas Society* (JPS) and the *Asian-Oceanic Pancreatic Association* (AOPA) joint meeting (IAP/JPS/AOPA) in Sendai, Japan on August 6, 2016.

During the 2016 EPC meeting, John P Neoptolemos, David C Whitcomb and Tooru Shimosegawa agreed on a joint venture to produce international consensus definitions and guidelines on CP with endorsement from the four International societies. The *Mechanistic Definition of CP* was used as a starting point, including a conceptual disease model that outlined a sequence of five disease stages representing the progression of CP from pre-disease state to end-stage features (10). The stages were defined as Stage A, "At Risk"; Stage B, "AP-RAP"; Stage C, "Early CP"; Stage D, "Established CP"; and Stage E, advanced or "End Stage CP". This progressive model was designed to organize the numerous biomarkers of disease state and disease activity within time frames, to aid in defining diagnostic criteria, disease subtypes, disease trajectory toward defined endpoints and effectiveness of treatments. Stage C, "Early CP" was included as a 'place-holder' while the minimum essential criteria for defining Stage C and Stage D were left for future discussions.

On August 6, 2016, a special session of the combined meeting of the IAP/JPS/AOPA was held in Sendai, Japan entitled "What is early chronic pancreatitis and why is diagnosis important?" Fourteen invited experts presented their perspectives on the question of "Early CP" based on a review of data from the relevant literature combined with their clinical experiences. The method of systematic literature review of major consensus reports, invited expert reviews, systematic reviews, and landmark papers that were published between 1965 and 2016 on recurrent acute pancreatitis (RAP) and CP was previously described (10). The international experts provided data and a range of opinions on multiple issues, and no overall consensus was reached. Subsequently at the joint IAP/Latin American Pancreas Club meeting in Buenos Aires in September 2017, it was agreed to consider 10 statements for which the level of consensus was determined.

Grading evidence

Prior to starting, the international experts were asked to vote on their preferred system for rating the quality of evidence, which would be used in the international guidelines recommendations. The decision was to use the Grading of Recommendations Assessment,

Development, and Evaluation (GRADE) approach, as adapted for "UpToDate" (http://www.uptodate.com/home/grading-tutorial). The quality of evidence supporting the ten statements was graded as (i) "high" if there was very low probability of further research substantially changing the conclusions, (ii) "moderate" if further research might completely change the conclusions, and (iii) "low" if further research was likely to completely change the conclusions.

Defining consensus

The ten statements were then voted on by the working group of international experts that participated in the meetings and discussions for strength of agreement, using a 9-point Likert scale. The results were used to calculate Cronbach's alpha reliability coefficient (http://hdl.handle.net/1805/344). The results were classified under "agreement" as either; strong (≥80% of votes were 7 or above), conditional (≥65% of votes were 7 or above), and weak (<65% of votes were 7 or above). In addition, explanatory comments were compiled to frame the issues surrounding the statement, supported by key references. The final results were tabulated. Based on these results a final draft of the document was generated and circulated to all the authors for final editing and approval.

Results

The ten statements (S) relating to ten questions (Q) for the definition and diagnostic criteria of Early-CP are provided with the consensus in respect of the quality of Evidence, strength of Recommendation and degree of Agreement, in addition to the Cronbach's alpha reliability coefficient ('alpha').

Q1. What is Early Chronic Pancreatitis?

S1. The term Early Chronic Pancreatitis describes the initial stage of definite chronic pancreatitis.

(Quality assessment: low; Recommendation: conditional; Agreement: conditional).

Alpha Agreement: 0.77

Explanation: Chronic pancreatitis is an acquired disease that occurs due to a variety of causes and has a progressive course. From a normal pancreas to a state of established chronic pancreatitis, the disease must progress through an intermediate state characterized by subtle features of CP regardless of clinical manifestations or pace of such progression.

Making a definite diagnosis of CP is important for several reasons. First, establishing a diagnosis provides answers to the patient as to the cause of signs and symptoms of disease that they may be experiencing. Second, it excludes or minimizes further diagnostic testing for other disorders within the differential diagnoses. Third, there is prognostic significance linked to the natural history of the disease. Fourth, it has management implications, both for symptomatic relief and limiting disease progression. Fifth, it triggers strong recommendations to avoid further alcohol or tobacco consumption.

A few of the working group members were concerned about the use of the term “definite” (suggesting that a critical number of yet-to-be-defined criteria need to make a diagnosis of CP had been met). Specifically, in the setting of subtle and/or non-specific imaging features a premature or inaccurate diagnosis of “definite” CP may result in inappropriate radical treatments such as total pancreatectomy with islet autotransplantation (TPIAT) (31).

It was generally agreed, but not unanimously, that if the diagnosis of Early-CP were based on imaging criteria alone, a “definite” diagnosis could not be made (See Statement 5). To some experts the term “Early CP” itself was incompatible with the term “definite” and should be considered equivalent to “Possible CP” or “Borderline CP”. In contrast, others argued that, in clinical context the term “Definite CP” is relative. It does not mean 100% accuracy, but rather an acceptable accuracy for the purposes of clinical classification. The idea of “acceptable” balances the concepts of *risk* versus *benefit* when making a “definite” diagnosis of CP (see Statement 6). It was further recognized that a subset of patients classified by imaging criteria as “Possible CP” who also have high-risk etiologic factors (e.g. highly pathogenic genetic mutations or heavy alcohol consumption), a clinical setting of AP or RAP might be classified as Early-CP. In contrast, other patients with similar imaging findings but without high-risk etiology factors or RAP should not be given a diagnosis of Early-CP, especially if other diagnoses have not been excluded such as IPMN or acinar cell cystadenoma (25).

The idea of “accurately” diagnosing CP prior to advanced imaging findings was considered “possible” by most of the working group under some conditions, such as in an individual with genetic risk, RAP and “some” features of CP on abdominal imaging (see Statement 6). However, since there is low quality of evidence to support this statement, only moderate consensus was reached (alpha 0.77).

There was agreement that future studies are required to confirm that CP can be accurately diagnosed by new approaches before the development of imaging features of Established CP and End Stage CP are detected. to meeting historically established imaging criteria. Until such time there may be some uncertainty associated with the diagnosis of Early CP because of various conditions that may cause similar histological or morphological changes in the pancreas, such as aging and diabetes (Table 2). The benefit of integrating the probabilistic advantages of genetic testing with documented environmental factors within appropriate clinical settings to define and accurately diagnose Early CP needs to be tested in prospective studies.

Q2. What does the word “Early” mean in the definition of Early Chronic Pancreatitis.

S2. The word “Early” in early chronic pancreatitis is used to describe disease state, not disease duration.

(Quality assessment: moderate; Recommendation: strong; Agreement: strong).

Alpha Agreement: 1.00

Explanation: Early CP is distinguished from Established CP and End-Stage CP by the absence of features of advanced CP (10). The rate of progression from Early CP to

Established CP and End-Stage CP varies greatly and the basis of the variation is unclear. It follows that the duration of Early CP cannot be defined.

Q3. What does the word “chronic” mean in the definition of Early Chronic Pancreatitis?

S3. The word “Chronic” in early chronic pancreatitis is used to describe disease character and duration.

(Quality assessment: moderate; Recommendation: strong; Agreement: conditional).

Alpha Agreement: 0.69

Explanation: The working group members disagreed on what the word “chronic” meant in the context of Early-CP. The work “character”, linked to the *Mechanistic Definition*, refers to the molecular characteristic of chronic injury or stress and/or the pathologic response to the *Injury* → *Inflammation* → *Resolution* → *Regeneration* sequence. Some working group members still believed that “character” refers more to the morphologic characteristics of more advanced stages as used in the Cambridge Score or the Established CP/End-Stage CP phases of the mechanistic definition. From this perspective they considered that this term was an ‘oxymoron’ in Early CP, as chronic morphologic features cannot occur at an early stage. Thus, the term “chronic” defined by features of the late stages of CP and applying it to Early CP may be misplaced.

To qualify for the term “chronic” pancreatitis on the basis of the *Mechanistic Definition*, there needs to be evidence of ‘a persistent pathologic response’ (10). This amounts to a dysregulation and pathologic persistence of the expected inflammation, recovery and regeneration sequence, and indicates an active and progressive pathogenic response linked to acinar cells and/or duct cells, depending on the underlying mechanism of injury or stress. Furthermore, these changes do not occur in the normal response to AP or RAP. There are, however, no widely accepted biomarkers that distinguish the response to AP and RAP from CP. Thus, the term “character” depends on the definition of CP, and the corresponding disease concepts and models.

The working group members offered different opinions regarding the term “duration”. The U.S. National Center for Health Statistics describes a chronic disease as one that last for three months or more, but the literature uses the term “chronic disease” variably and it depends on the data used for the research and the discipline of the lead authors (32). There were some members of the working group that agreed that a period of persistent pathologic response for greater than 6 months after AP or RAP was a reasonable and pragmatic threshold for the diagnosis of Early CP while others advocated for at least 12 months. Some also argued that within that time frame (6 or 12 months) there should be detection of “at least some” morphological features diagnostic of Established CP but not enough for definitive diagnosis of CP.

Q4. How does Early Chronic Pancreatitis affect pancreatic function?

S4. Early chronic pancreatitis defines a stage of CP with preserved pancreatic function and potentially reversible features.

(Quality assessment: low; Recommendation: strong; Agreement: strong).

Alpha Agreement: 0.83

Explanation: There are two components to this statement. Preserved pancreatic function means that viable parenchymal tissue remains that can function in terms of generating pancreatic digestive enzymes from acinar cells and secreting a bicarbonate-rich fluid from the duct cells. Secondly, the Early CP stage *may be* early enough that some of the lost functional features may return with appropriate treatment. The first concept recognizes a gradient from normal function to complete loss of function or organ failure, with the Early CP stage being closer to normal. The second concept is more difficult, because it suggests that there is a point in CP severity where the damage is irreversible and there is no chance of recovery.

There is little clinical evidence for the reversibility of impaired pancreatic function (or fibrosis) in CP, although this remains a research aim in developing therapies targeting the drivers of CP. However, there are several observations which suggest the potential for reversibility in Early-CP

First, in humans, viral hepatitis may lead to liver fibrosis (cirrhosis) and liver failure. However, new therapies for hepatitis B and hepatitis C that eliminate the virus can result in reversal of fibrosis and improvement in liver function (33–36). Histological regression of cirrhosis occurs in only a subset of patients and regression is more likely if the fibrosis occurred more recently, if there is effective and long-lasting viral suppression, if there is internal capacity to regenerate and if there is no vascular thrombosis (33). Regression of fibrosis also occurs in patients with common bile duct stenosis after biliary drainage (37). In the liver, elimination of the source of injury is the primary condition needed for the regression of cirrhosis, and patients with regression have better clinical outcomes than those who do not (36–38). These data indicate that reversal of fibrosis in humans is possible, and that in some cases of liver disease, function is at least partially restored.

Second, in animal models of CP, recurrent injury to the pancreas with cerulein-induced hyperstimulation to causing AP and RAP leads to pancreatic fibrosis (39–42). Discontinuing cerulein injections leads to resolution of the fibrosis and regeneration of normal pancreatic tissue, depending on the severity of damage over time (39). This observation indicates that elimination of the inflammatory driver at earlier stages can lead to regression in experimental models pancreatic fibrosis.

Third, there are conditions in humans in which exocrine pancreatic insufficiency resolves. Patients with autoimmune pancreatitis may have exocrine and/or endocrine pancreatic insufficiency, and these insufficiencies improve after steroid therapy (43), showing that the functional loss is reversible. Finally, pancreatic insufficiency is seen after AP, and generally reverses during recovery (44, 45). EPI may persist after AP in up to a third of patients (46–50), but in some cases the EPI resolves with time (51).

This statement therefore defines the concept of reversibility, within limits, of lost exocrine function in Early CP. Future studies are needed to determine whether there are specific

subtypes of CP that have a component of reversible pancreatic functions with targeted therapies. The line between reversible and irreversible function loss has yet to be determined, but will vary depending on the number of factors including the particular function, the severity of functional impairment and the efficacy of the treatment.

Q5. Can Early Chronic Pancreatitis be diagnosed by abdominal imaging techniques alone?

S5. Early Chronic Pancreatitis cannot be diagnosed based on currently available imaging techniques alone.

(Quality assessment: moderate; Recommendation: strong; Agreement: conditional).

Alpha Agreement: 0.77

Explanation: Continuing improvement in abdominal imaging techniques have allowed more subtle changes in pancreatic structure to be detected. And while these imaging features are taken as surrogate for histological changes such as fibrosis, these findings are nonspecific (25). Many imaging features of Early CP overlap with other conditions associated with mild fibrosis, atrophy or altered morphology including old age, long-standing diabetes mellitus, alcohol abuse without AP, and smoking without AP (52–54) (Table 2). EUS is considered the most sensitive modality for detecting Early CP (19, 23), although the number and type of diagnostic criteria continue to be debated (55). EUS does offer quantitative measures that are useful for staging severity of structural changes, calcifications, and fibrosis, especially when coupled with elastography (56–60). Furthermore, some patients with definite CP on histology have “normal” EUS using Rosemont criteria for CP (8). However, in general, as the threshold number of EUS criteria increases, the specificity for a diagnosis of CP increases but the sensitivity decreases (61). Since current imaging technology cannot measure and differentiate between the various pancreatitis-related or other etiologies of inflammation or fibrosis, it cannot be recommended for this purpose.

In contrast, some of the working group members argue that the Early-CP can be diagnosed by EUS criteria in the hands of expert physicians. Others suggested that although Early-CP cannot be diagnosed by abdominal imaging techniques now, it may be possible in the future as technology advances, especially with inclusion of functional measures. Future prospective studies are required to determine the accuracy of diagnosing Early CP in populations with patients with other disorders with similar or overlapping imaging features.

Q6. Can Early Chronic Pancreatitis be diagnosed by a combination of factors?

S6. Theoretically Early CP can be diagnosed based on a combination of (a) the presence of high risk factors for CP, (b) low risk for other disorders with features that overlap CP, (c) appropriate clinical context and (d) supportive biomarkers

(Quality assessment: low; Recommendation: strong; Agreement: weak).

Alpha Agreement: 0.62

Explanation: The working group could not reach consensus on the diagnostic criteria for Early CP, although there was general agreement that it should be possible to make a fairly accurate diagnosis with the right combination of yet-to-be-determined criteria. There was agreement that some clinical features favored the diagnosis of CP, while other features either favored alternative diagnoses, or were nonspecific (Table 1). The working group also agreed that in addition to a combination of risk factors associated with CP, the clinical context and supportive biomarkers were all necessary to establish a "probable" diagnosis of Early CP. However, there was only a moderate level of consensus for the statement that a "definitive diagnosis" of Early CP could be made (see Statement 1 discussion).

Currently, a diagnosis of CP using imaging criteria is possible when there are advanced morphologic changes, but this precludes a diagnosis of early CP. The problem with using morphology as the sole diagnostic criteria for CP is that imaging findings do not correlate with pain, with disease activity or important outcomes (62, 63). This is especially important because clinical management of pancreatitis patients typically focuses on inflammation, pain and dysfunction rather than on fibrosis. Thus, the tradeoff of using advanced features of the Cambridge Score for a "definitive" diagnosis of CP is very low sensitivity for earlier phases of CP in exchange for higher specificity late in the disease. An alternative approach is needed that will improve both sensitivity and specificity.

Given that morphological features cannot be relied on for the accurate diagnosis of Early CP, other factors will be necessary. The hope is that the mechanistic definition of CP (10), which takes into account risk factors, biomarkers of inflammation, pain and functional status within the clinical context, will provide a framework for the development of diagnostic criteria that will allow the accurate diagnosis of Early CP.

Biomarkers objectively measure and biological and pathogenic processes (64, 65). Biochemical analytes, pain scales, imaging features, function tests and histology can each be used as biomarkers of different aspects of pancreatic health or disease to determine disease stage, state, trajectory or response to treatment. Since RAP and CP are complex disorders affecting multiple systems with variable responses, one biomarker, such as a pancreas image, cannot serve as a surrogate for all other biomarkers. Biomarkers without a defined context are also problematic since they are typically derived from naturally occurring features that become abnormal through statistically significant (+/− standard deviation) changes from normal in location, amount or timing of the feature. Thus there are inherent challenges with sensitivity and specificity; especially since specificity calculations are dependent on the population within which the biomarker is tested (66). Indeed, the issue of specificity raised the most concern among the working group members that opposed supporting a diagnosis of Early CP using imaging criteria alone.

The mechanistic definition of CP includes risk factors as a central part of the definition. Unlike biomarkers, risk factors are attributes, characteristics, or exposures that increase the likelihood of developing an injury or disease. A number of risk factors for CP, and the relative risk or risk ratio (RR) for many of these factors have been calculated (3, 67–69). Selecting patients with high risk effectively increase the prevalence of disease within the population being evaluated (70) and therefore improves the positive predictive value of the

biomarker-based test. Excluding patients with other disorders further increased the accuracy by removing potential false positive individuals. The probability that a biomarker of Early CP can provide and accurate diagnosis is influenced by the clinical context, and in particular the presence of risk factors. For example, a history of heavy alcohol use or RAP will increase the accuracy of a diagnostic biomarker of Early CP

Q7. Is acute pancreatitis a mandatory risk factor for Early Chronic Pancreatitis?

S7. A history of acute pancreatitis, and especially recurrent acute pancreatitis, are significant risk factors for early chronic pancreatitis, but are not mandatory to make a diagnosis.

(Quality assessment: low; Recommendation: conditional; Agreement: weak).

Alpha Agreement: 0.62

Explanation: Animal models of CP, clinical case series and multiple epidemiological studies have established that AP often, but not always, precedes CP (47, 49, 50, 71–75). It is generally accepted that AP is associated with the sequence of *Injury* → *Inflammation* → *Resolution* → *Regeneration* (10). The likelihood of CP developing is higher in patients with previous RAP than previous AP (76). Since AP and RAP are both major risk factors for CP, it follows that AP and RAP are also risk factors for Early CP. The members of the working group agreed that evidence for a diagnosis of Early CP was strengthened by a history of AP and especially RAP. However, some members of the working group felt that prior AP or RAP *should* be mandatory to make a diagnosis of Early CP. The likelihood that imaging features of mild pancreatic fibrosis represents Early CP is low in the absence of a history of AP. The relationship between the severity and timing of AP and the likelihood and timing of Early CP is unknown. The working group agrees that a careful history and documentation of risk factors such as a TIGAR-O list (9, 23, 77, 78), previous episodes of AP/RAP and their severity should be documented in all patients suspected to have CP.

Q8. Are genetic variants a required risk factor for Early Chronic Pancreatitis?

S8. Genetic variants are important risk factors for early chronic pancreatitis, but they are neither necessary nor sufficient to make a diagnosis.

(Quality assessment: moderate; Recommendation: strong; Agreement: strong).

Alpha Agreement: 0.85

Explanation: The discovery of high-risk, high penetrant and highly specific germ line mutations that can cause CP supports their use in the diagnosis of Early CP, especially as they are present before the onset of symptoms. The use and interpretation of a genetic test to evaluate a patient with possible Early CP is different in several ways than genetic testing in other settings. First, the testing is not done in asymptomatic patients to calculate life-long risk of developing a disease. Secondly, it can be used to determine which physiologic process is likely dysfunctional (e.g. duct secretion, trypsin regulation, unfolded protein response, oxidative stress). Third, evaluation of pathogenic modifier gene variants can be used to assess risk of more rapid progression to later stages of CP and complications (e.g.

CTRC linked to high risk with smoking (79), or *CLDN2* linked to high risk of progression, especially with continued alcohol consumption (80–82)). Fourth, identification of pathogenic genetic variants in a symptomatic patient may identify the etiology of AP/RAP or pancreatitis-like symptoms and preclude the need for further workup. Finally, genetic testing is becoming important in identifying variants that predict response to specific genetic variants such as *CFTR* (83–86). Thus, in symptomatic patients genetic testing is not only valuable in determining the likelihood of Early CP, in contrast to other disorders, but it can also provide information on disease mechanisms and potential therapeutic targets.

Limitations in the availability and understanding of genetic data make obtaining a clear and accurate interpretation of individual genotypes challenging (87). Current genetic testing options contain a number of inherent challenges, including genotyping only a limited number of genes with small gene panels, incomplete coverage of key genes by focusing on a single nucleotide polymorphisms (SNPs), high homology between target genes, homologues and pseudogenes (88), and inability to detect many insertions, deletions, tandem repeats, copy number variants and fusion genes (89–92). In contrast, larger gene panels or exome/genome sequencing provide more data but also identify greater numbers of variants of unknown significance and may miss correct sequencing of homologous or repeat regions.

The complexity of the CP syndrome is such that subsets of patients possess one or more highly pathogenic genetic variants associated with pancreatitis, while others have no identifiable genetic risk and yet develop End-stage CP. As with many disorders with a genetic component, physicians are faced with the burden of evaluating and managing genetic variants of unknown significance, and must recognize that there are likely many additional pathogenic variants yet to be discovered. Furthermore, genetic results cannot be interpreted outside of the clinical context, and the context of pancreatic diseases is complex. Genetic counseling is also important, both for the patient, and to help physicians who have a limited background in genetics or do not have the time to stay up to date with this dynamic field. However, the genetic counseling framework must be adapted for a complex disease when testing is used to evaluate the contribution of multiple modifiers that drive disease, rather than a Mendelian trait (93). Genetic testing can provide strong evidence of the etiology for RAP and Early CP, and help determine the mechanism of an evolving disease. Therefore, in the evaluation of Early CP, genetic testing for pancreatitis susceptibility genes and disease modifier genes in patients with RAP or evidence of Early-CP is clinically indicated when available (26, 78, 94), and should include both susceptibility genes and modifier genes with appropriate counseling.

Q9. Are environmental factors required risk factors for Early Chronic Pancreatitis?

S9. Environmental risk factors can provide important evidence in favor of early chronic pancreatitis, but they are neither necessary nor sufficient to make a diagnosis.

(Quality assessment: moderate; Recommendation: strong; Agreement: strong).

Alpha Agreement: 0.92

Explanation: The presence of environmental factors in the right clinical setting highly supports the diagnosis of Early CP. The best studied environmental risk factors for chronic pancreatitis are heavy persistent alcohol use and cigarette smoking, and the effects are additive (95–98) (99). However, the majority of individuals with heavy or very heavy alcohol use do not develop chronic pancreatitis (100).

Both alcohol and smoking have direct effects on the pancreatic acinar and duct cells. Furthermore, during heavy use there are parenchymal changes in the pancreas that can be detected by image techniques such as endoscopic ultrasound (52, 54, 101, 102). In one study about 4% of healthy asymptomatic people without history and/or signs of pancreatic disease had at least three or more EUS abnormalities consistent with the diagnosis of CP (54). However, most of these changes stabilize or may resolve with cessation of the risk factor (103, 104). It is not known whether these features represent Early CP with resolution following elimination of the disease driver or whether they represents non-specific changes.

Persistent alcohol use and smoking are important but nonspecific risk factors for CP since some parenchymal changes can be seen that may not fulfill diagnostic criteria for CP using the Cambridge Scale. Use of predictive models that include genetic testing and history of AP or RAP may be helpful in classifying these patients in the future, but these clinical studies are lacking. The committee members and working group agree that during evaluation, a careful qualitative and quantitative history of alcohol and smoking use is required, and this information may increase the accuracy of a diagnosis of Early CP. The factors that define and drive the early fibro-inflammatory response require further study.

Q10. What is the *differential diagnosis* for Early Chronic Pancreatitis?

S10. The differential diagnosis for Early CP includes any other disorder with features that overlap the features of chronic pancreatitis as defined in the Mechanistic Definition of chronic pancreatitis.

(Quality assessment: moderate; Recommendation: strong; Agreement: strong).

Alpha Agreement: 0.83

Explanation: There are many disorders that result in changes in structure, function, clinical signs and symptoms and biomarkers that are similar to those that are thought to be present in Early CP. This overlap makes definitive diagnosis of Early CP difficult (4, 24, 25). The probability that early changes are due to Early CP is directly related to the likelihood of CP and inversely related to the likelihood of other disorders. The Mechanistic Definition defines the CP as a result of injury or stress (arising from the acinar cells or ducts) that generates a persistent inflammatory response (4, 24). This definition excludes autoimmune inflammation, inflammation and fibrosis arising from the islets related to long-standing diabetes mellitus, renal disease causing secondary effects on the pancreas, medications that alter the immune system (e.g. cyclosporine), age-related atrophy or fibrosis, IPMN, acinar cell cystadenoma, the desmoplastic response to pancreatic neoplasm, inflammation upstream of a duct obstructing mass, etc. Examples of the features that favor CP, or another diagnosis are nonspecific are listed in Table 2.

In the future, clinical studies on patients evaluated for Early CP should also include the diagnostic tests and biomarkers that were used to address the differential diagnoses and clarify the true etiology of the underlying signs and symptoms. Such data will be useful for guiding future recommendations and guidelines.

Discussion:

The concept of Early-CP is well established, but there are no established definitions or diagnostic criteria. The goals in defining and developing specific criteria for Early CP are to facilitate the early and accurate diagnosis of the underlying disease so that effective, mechanism-based therapies can be developed, to minimize or reverse early disease features and to avoid late stage complications and poor outcomes (4, 25). A secondary effect is the avoidance of further unnecessary diagnostic testing, stopping inappropriate treatments and selecting better therapies. Early CP cannot be diagnosed by current imaging technologies alone and requires a new approach. In addition to imaging features the clinician must consider genetic and environmental risk factors, other biomarkers and functional tests, the clinical history and the clinical context. However, application of these concepts into practice is proving to be difficult. International consensus on the definition and criteria for diagnosing Early CP continues to be needed.

Central to the criteria for diagnosing any disorder is consideration of the risk: benefit ratio for doing the testing (e.g. EUS, ERCP) and implementing treatment (e.g. surgery, TPIAT) versus an alternative treatment or expectant observation until the disorder “declares itself”. If the outcome to be avoided is fibrosis, say in 10 years, and there is no specific therapy, then observation and symptomatic treatment may be indicated. If the outcome is severe pain and treatment delay results in continued suffering and high likelihood of developing an untreatable chronic pain syndrome, then early diagnosis and definitive treatments may be very beneficial (11, 105). The type of treatment planned for the *current* stage of the disease and severity of symptoms must also be evaluated. For example, the impact of treating a patient with Early CP with antioxidants (linked to a daily cost and inconvenience) is low, while the cost of treatment with surgery or TPIAT is high and the treatment is irreversible. Also, some treatments such as antioxidants appear to be more effective when started early (106). Other examples such as amlodipine (107) or camostat (108) may have positive effects but adequate studies are lacking and/or they may not be widely available. New clinical studies, utilizing new diagnostic approaches and designs are needed to provide evidence for future guidances.

The current report documents the level of agreement among international experts on various concepts related to Early CP. There was strong consensus on several statements including (Statement 2) the meaning of the word “Early”, (Statement 4) preserved pancreatic function and potentially reversible features, the importance of considering (Statement 8) genetic and (Statement 9) environmental etiologies and (Statement 10) on the differential diagnosis. Statements with moderate or low consensus included making a “definite” diagnosis of CP at earlier stages than currently available with the imaging criteria such as the Cambridge Score (Statements 1 & 6). Only moderate consensus was achieved with the definition of “chronic” in Early CP (Statement 3) and the interpretation and relative importance of imaging features

(Statement 5). Furthermore, distinction between Early CP, probable CP, borderline CP and possible CP remains unclear, as does the implications of the use of these terms. However, Early CP could potentially be diagnosed, with a high degree of accuracy (i.e. not 100% denoting “definite”), using a combination of (a) identification of high risk factors for CP, (b) the absence of high risk factors for other disorders with features that overlap CP, (c) appropriate clinical context and (d) supportive biomarkers including imaging as proposed by the JPS. Depending on the purpose of the test (low or high risk intervention), the threshold for diagnosis could be set to maximize sensitivity and/or specificity. This requires prospective evaluation since at the present time our test panels lack the necessary accuracy for routine clinical practice.

Without a definition or diagnostic criteria for Early CP it has not bee possible to conduct high quality prospective studies. Several preliminary studies provide an estimate of the progression from Early CP to Established CP. In Japan, 113 patients with “Early CP” based on clinical factors and EUS and ERCP findings (based on the JPS 2010 Guidelines, Japanese Diagnostic Criteria 2009) (4) were recruited by 13 member institutes of the Japanese Research Committee of Intractable Pancreatic Diseases (RCIPD) by 31 December 2010 and followed up to 31 December 2012(T Shimosegawa, Report of the RCIPD, 2014). Five (9.6%) of these 52 patients progressed, 15 (28.8%) were unchanged and 32 (61.5%) improved. The diagnosis using the same guidelines two years later was “Definitive CP” in 2, “Probable CP” in 3 “Early Suspected CP” in 6 and ‘No symptoms” in 26 (109). Thus uncertainty as to any diagnosis of CP remained in over 50% of cases diagnosed with “Early CP” more than two years earlier. Partly based on these findings the JPS Guidelines altered the diagnostic criteria to include Clinical/Functional features as shown in Table 1 and Figure 1 (24).

A 20-year study from Liverpool identified 40 (17%) of 807 patients with CP, with the findings of minimal change chronic pancreatitis (MCCP) or “Early CP” based on clinical factors and EUS findings. On follow-up only 12 (30%) went on to develop radiological and/or histological features of definite CP, with a median follow-up of 30 (IQR, 18.75–36.5) months. Five (12.5%) had complete regression of MCCP changes and the remaining 23 (57.5%) demonstrated no progression of radiological features to support a diagnosis of CP (110). These studies emphasize the need for better initial diagnostic criteria and prospective tracking of patient trajectory in larger cohorts.

In contrast to patients presenting with EUS findings as the initial sign of CP, Skinazi et. al. (111) followed 114 alcoholic patients without CP who presented with an initial attack of acute alcoholic pancreatitis and were followed prospectively for a minimum of two years. Definite CP was identifying in 101 patients (88.6%) by a combination of pancreatic calcifications (n = 71), mild to severe imaging abnormalities (n = 19), histological examination (n = 8), and perioperative data (n = 3). Four additional patients (3.5%) developed DM as the primary clinical feature along with sufficient clinical and imaging evidence to classify them using traditional criteria as Probable CP. This prospective study confirms the link between AP and CP, and documents the high risk of progression from AP to CP in patients with alcoholism.

One of the major challenges for clinicians is to make a diagnosis in patients with or without a history of AP who have persistent exocrine pancreatic insufficiency, pancreatic atrophy, post AP diabetes mellitus, or recurrent-persistent abdominal pain following AP without *morphologic* changes of advanced CP. In some cases clinicians have diagnosed these patients as “minimal change CP” or “atypical CP” (112, 113). The opportunity to conduct future studies that utilize risk profiles, biomarkers of pancreatic injury or stress, tissue analysis when available, responses to targeted treatment and outcomes may resolve these questions. Better definitions of Early CP, facilitated by the mechanistic definition that helps identify the underlying disease drivers and potential therapeutic targets is an excellent example of precision medicine. This more holistic and individualized approach should lead to a more accurate diagnosis of patients with Early CP, and facilitate prospective studies that better define the natural history, rates of progression and more homogenous cohorts for intervention studies. It is clear that the approach to the definition and diagnosis of Early CP cannot be dependent on morphological changes.

Conclusions.

New approaches to the definition and diagnosis of Early CP should use risk factor analysis, biomarkers, clinical context and new models of disease with assessment of overall sensitivity and specificity integrated with risk: benefit analysis of treatment. Because these concepts are new, well-designed prospective clinical studies with long-term follow-up need to be conducted.

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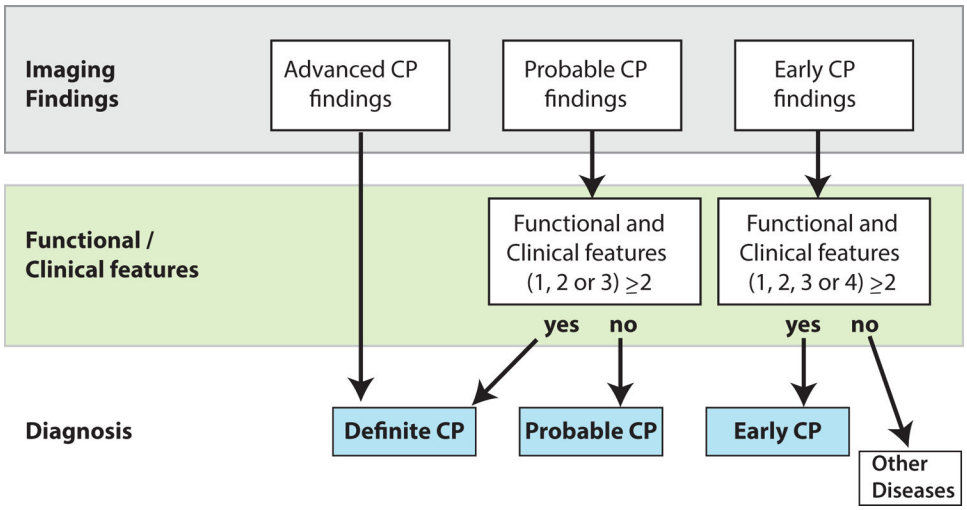

Figure 1.

Method of diagnosis Definite CP, Probable CP and Early CP using the Japanese Pancreas Society Clinical Guidelines, 2015. Clinical and imagine features of early CP are in Table 1. Modified from Japanese clinical guidelines 2015, Ito, et al (24).

Table 1.

Early CP diagnosis from the Japanese clinical guidelines 2015.

A. Clinical/Functional Features.	
1	recurrent upper abdominal pain (two or more attacks)
2	abnormal serum/urine enzyme levels,
3	abnormal exocrine function, with an additional criteria for Early CP of
4	continuous heavy drinking (> 80g/d).
B. Imaging findings of early chronic pancreatitis (either a or b)	
a.	More than two among the following seven features of EUS findings including at least one of (1–4)
1.	Lobularity with honeycombing
2.	Lobularity without honeycombing
3.	Hyperechoic foci without shadowing
4.	Stranding
5.	Cysts
6.	Dilated side branches
7.	Hyperechoic MPD margin
b.	Irregular dilatation of more than three duct branches on ERCP

EUS endoscopic ultrasonography, MPD main pancreatic duct, ERCP, endoscopic retrograde cholangiopancreatography

Table 2.

Factors affecting the likelihood of CP. AP, acute pancreatitis; CP, chronic pancreatitis; DM, diabetes mellitus; EPI, exocrine pancreatic insufficiency; IPMN, intrapancreatic mucinous neoplasm; PDAC, pancreatic ductal adenocarcinoma; RAP, recurrent acute pancreatitis; SDS, Shwachman-Diamond Syndrome.

Pancreatology		
Favors CP	Favors other Dx:	Nonspecific
CP Genetic Risk Factors	Longstanding DM (e.g. >5 years before first AP)	Alcohol Use (without AP)
CP Genetic Modifiers	Older age	Tobacco Smoking (without AP)
Acute Pancreatitis	Renal disease (advanced)	
RAP	Drugs (e.g. cyclosporine)	
Characteristic Pain	Elevated IgG4	
Chronic alcohol abuse and/or smoking (with AP)	High risk of PDAC	
	IPMN	
	EPI disorders (e.g. SDS)	