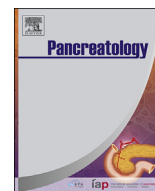




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# International consensus statements on early chronic Pancreatitis. Recommendations from the working group for the international consensus guidelines for chronic pancreatitis in collaboration with The International Association of Pancreatology, American 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  $\geq 0.80$ .

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**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.

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## 1. 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.

### 1.1. 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 AP and CP, 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].

### 1.2. ‘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

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