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Diagnosis of Chronic Pancreatitis

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Abstract: Chronic pancreatitis (CP) is a clinically defined, usually progressive chronic inflammatory disease of the pancreas based on a combination of signs and symptoms. Current criteria for diagnosis rely on overt moderate-severe morphologic changes on cross-sectional imaging. Late-stage disease is an irreversible condition associated with lost pancreatic function and complications that lead to poor quality of life (QOL). Historically treatment is symptomatic, supportive and often ineffective. This article describes our approach to the diagnosis of CP and discusses the limitations of current diagnostic criteria. Clinical unmet needs include reliably making a diagnosis of early stages of CP, accurately predicting disease progression and establishing biomarkers of different stages of CP. Addressing these needs will offer an opportunity for targeted approaches to prevent progression to end-stage disease.

Key words: Pancreatitis, inflammation, fibrosis, trypsin, lipase, exocrine pancreatic insufficiency, diabetes.

Outline:

1. Introduction

Chronic pancreatitis (CP) is an irreversible chronic inflammatory disease of the pancreas that over time leads to exocrine and endocrine dysfunction in most patients. The classic triad of CP includes: (a) calcification in the pancreas on abdominal X-ray, (b) diabetes mellitus (DM) and (c) steatorrhea, is typically seen in patients with alcoholism and heavy smoking. Currently, the diagnosis of CP relies heavily on imaging findings with clinical signs of organ dysfunction that reflect an advanced stage of disease and etiologic factors with a high risk of CP contributing to the overall assessment. Diagnosis of CP at an earlier stage is important so that strategies to prevent progression can

Abbreviations used in this paper. CECT, contrast-enhanced computed tomography; CP, chronic pancreatitis; DM, diabetes mellitus; EPI, exocrine pancreatic insufficiency; EUS, endoscopic ultrasound; HbA1c, hemoglobin A1C; MRCP, magnetic resonance cholangio-pancreatography; MRI, magnetic resonance imaging; NAPS2, North American Pancreatitis Study II; PDAC, pancreatic ductal adenocarcinoma; sMRCP, secretin enhanced MRCP; RAP, recurrent acute pancreatitis; TPIAT, total pancreatectomy with islet auto transplantation

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be identified and justified.[1] However, early diagnosis is difficult as advanced morphologic changes may not be apparent on cross-sectional imaging and most cases of suspected early CP do not advance to end-stage CP. The gaps in knowledge include our ability to identify prevalent CP in patients who have suggestive clinical presentation or are at high-risk of disease progression, to predict disease course, and to identify accurate biomarkers for different stages of CP. Until additional research and consensus on systematic approaches are reached, the traditional approach to diagnosis of CP remains as the standard of care.

Our general approach to evaluation and management of CP from the perspective of a pancreatologist is published.[2] Evaluation includes taking good history of symptoms, personal and family history, risk factors and review of laboratory test results (**Table 1**).

The diagnosis of CP is established by the presence of definitive changes in the pancreatic parenchyma and/or ductal system on cross-sectional imaging, i.e. contrast-enhanced computed tomography (CECT) scan of the abdomen and/or magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography (MRCP), preferably with secretin injection. In select patients where the clinical presentation is convincing but cross-sectional imaging does not show obvious morphologic changes, an endoscopic ultrasound (EUS) is performed.

Table 1. Clinical characteristics of CP

Symptoms
- Abdominal pain
- Recurrent acute pancreatitis
- Diarrhea and/or steatorrhea
- Weight loss
- Diabetes
- Jaundice

Laboratory testing
- Abnormal serum amylase and/or lipase levels
- Elevated liver injury test tests
- Elevated blood sugar and Hemoglobin A1c levels
- Low fecal elastase-1
- High quantitative (24 hour) fecal fat
- Vitamin deficiencies (e.g. fat-soluble vitamins, vitamin B12)

Imaging features
- Duct distortion, strictures and dilatation
- Calcifications (parenchymal, ductal)
- Gland atrophy
- Common bile duct stricture
- Local complications – necrosis, pancreatic/peripancreatic fluid collection(s), pseudocysts

Table 2. Genetic variants associated with CP*

Recurrent acute pancreatitis in the trypsin-dependent pathway

Acinar Cell
- *PRSS1* (hereditary pancreatitis)
- *SPINK1/SPINK1* (familial pancreatitis)
- *CTRC* (variants reducing gene expression, sporadic)

Duct Cell
- *CFTR / CFTR* (cystic fibrosis, CFTR-related disorders)

Mixed
- Complex acute pancreatitis risk genotypes (*CASR, CFTR, CTRC, PRSS1/2,* etc)

Extra pancreatic:
- Genetic risks for gallstone disease linked to AP and RAP (polygenic risk, sex, BMI)
- Hypertriglyceridemia risks (polygenic risk and environmental factors)

Chronic pancreatitis risks

Genetic variants in the protein misfolding pathway
- *CEL, CPA1, CTRC, PRSS1*, etc)

Genetic variants in the cellular injury response pathway
- *GGT1* (oxidative stress in the duct cells*)*
- *UBR1* (unfolded protein response and secreted protein ubiquitination pathway)

Genetic variants affecting severity of inflammation
- *PRSS1/2* locus (10kb insertion variant including T cell receptor B (*TRB*) variants increasing fibrosis response and *PRSS2* promoters increasing *PRSS2* expression.[4])
- *CLDN2* (Alters endothelial CLDN2 expression and leukocyte adherence promoting inflammation. [5])

(continued)

Confounding condition risks

Diabetes mellitus
- Polygenic risk for Type 2 DM and others

Chronic pain syndromes
- Depression and anxiety genes[6, 7]
- Chronic pain genes
- Pharmacogenetic factors

Celiac disease
- Increases risk for CP
- Confounds assessment of exocrine pancreas insufficiency.

*This list is a high-level overview of common genetic risk. Genes are listed by symbols only. In many cases only *PRSS1, CFTR, SPINK1* and *CTRC* gene variants are tested and interpreted within a Mendelian genetic framework rather than a precision medicine (complex disease modeling) approach.

The extent of evaluation for the etiology of CP depends on history and clinical presentation. A summary of risk factors and etiologies of recurrent acute pancreatitis (RAP) and CP are given in the TIGAR-O list.[3] Testing for pathogenic variants in pancreatitis susceptibility genes (**Table 2**) is performed in patients without an obvious etiology and in those in whom the reported amount of alcohol consumption does not explain the disease. The utility of genetics in understanding the complexity of the pancreatitis syndromes is considered in the section on the role of genetics in the etiologic diagnosis of CP.

In patients with a confirmed diagnosis of CP, endocrine and exocrine function is evaluated by blood sugar and hemoglobin A1c levels and exocrine function by fecal elastase-1 testing. We currently do not routinely perform endoscopic pancreatic function testing in our practice. Testing for vitamin D, vitamin B12 and bone density is also performed (**Table 3**).

The diagnosis of CP continues to be established based on *definitive* changes in the pancreatic parenchyma and/or ductal system on cross-sectional imaging in patients.

Table 3. Laboratory and imaging tests at the time of diagnosis and during follow-up in patients with CP

- Hemoglobin A1C (HbA1c), blood glucose (preferably fasting) – at diagnosis and every 6-12 months
- Fecal elastase-1 – at diagnosis and then as needed
- Quantitative fecal fat – in select cases, as needed (seldom used clinically)
- Serum vitamin D, B12 – at diagnosis and every 6-12 months
- Liver function panel, including serum albumin, total protein – at diagnosis, yearly and as needed
- DEXA Scan – at diagnosis and every 3 years
- Imaging tests (CT scan, MRI/MRCP) – as needed (including screening for sarcopenia)

Probable CP.

In select patients with a high suspicion for CP, e.g. a patient with AP or RAP who has developed chronic abdominal pain, but cross-sectional imaging does not show morphologic changes of CP, a clinical diagnosis of "probable CP" is made with an expectation that during longitudinal follow-up definitive changes of CP will become evident on cross-sectional imaging to confirm the suspected diagnosis.[1, 8, 9] The problem is that the time between onset of symptoms and progression to CP can be prolonged to up to a decade.[8] Another issue is that there is no diagnostic code for this "probable CP" among ICD-10 codes so diagnostic codes for other established features must be used. Furthermore, the positive predictive value for ICD-10 code-based diagnosis of verified CP using electronic health records is only 54.5%[10], indicating that more accurate diagnostic criteria are needed along with improved coding.

In selective patients suspected to have CP but pancreatic imaging does not demonstrate characteristic changes, a diagnosis of "Probable CP" is made.

Patient education remains a central tenet of successful treatment. Taking the time to help patients understand the etiology and driving factors of their disease is important for many reasons. High among these is to provide some answers as to why the patient developed this condition, natural history of disease and to ensure their full participation in the treatment plan.

Diagnostic criteria: Current approach and limitations

Patients with evidence of CP on abdominal imaging.

Findings suggestive of CP on abdominal imaging include parenchymal and ductal changes such as calcifications, ductal dilatation, ductal stricture(s) and pancreatic atrophy. Currently, the diagnosis of CP relies on cross-

sectional imaging (CT scan and/or MRI/MRCP) with evidence of changes related to chronic inflammation and fibrosis.[1, 11, 12] Imaging of the pancreas is used as a surrogate for underlying pathology (e.g. Cambridge criteria)[13] since routine biopsies of the pancreas at one or more locations has risks of pancreatitis, infection or pancreatic fluid leak. Multiple attempts to diagnose CP with EUS have been proposed[14-16], but interobserver variations, disagreement on the type and number of criteria for early diagnosis and questions as to specificity of findings of fibrosis being CP continue to be major limitations.[1, 17-20] The limitations of currently accepted diagnostic criteria is that the imaging findings must be sufficiently advanced before a definitive diagnosis can be made.

Imaging evidence of CP includes a *combination* of changes related to significant fibrosis (e.g., dilation of pancreatic ducts), calcifications, pseudocyst (suggesting previous AP) and atrophy. Isolated finding of many of these features alone may be nonspecific.

Patients with clinical evidence of CP without significant changes on abdominal imaging.

The presence of definitive changes on imaging studies helps to establish the diagnosis of CP. However, a subset of patients in whom the clinical features are suggestive of CP likely *have* underlying CP, but due to the absence of obvious morphologic changes, making a diagnosis of CP is difficult based on current consensus diagnostic criteria. Several terminologies have been used for this clinical scenario, including "Early CP" and "Minimal change CP". Approaches used in clinical practice for diagnosis in this situation include evaluation for parenchymal and ductal changes on EUS[18], MRI/MRCP[21-23], secretin enhanced MRCP (sMRCP)[24] and assessment of bicarbonate concentrations in duodenal aspirate after secretin stimulation using traditional (Dreiling's tube) or endoscopic approach.[25-27] Comparisons between these approaches have been made in cross-sectional studies[28-30] and some studies have made comparisons with histology in patients undergoing total pancreatectomy with islet auto transplantation (TPIAT).[31] On EUS, which some consider the most sensitive modality for evaluation of the pancreas[17], the presence of five or more ductal and parenchymal features are considered to be consistent with CP, while fewer are considered inconclusive. Limitations of EUS include its subjective assessment, interobserver variability and the likelihood of features considered to be surrogate for fibrosis on histology to represent non-specific changes as they can also be seen in the absence of CP.[32]

The diagnosis of CP in patients with compelling clinical characteristics, risk factors and/or biomarkers, but without imaging changes is difficult and often cannot be made without histology of the gland. Advanced imaging techniques and better biomarkers are needed.

Fibrosis alone is not pathognomonic of CP.

Fibrosis is a response of the immune system to stress. In the pancreas, fibrosis is mediated by pancreatic stellate cells.[33, 34] The deposition of fibrosis in the pancreas by stellate cells is not specific to pancreatitis since, as an example, the fibrotic process is very robust in pancreatic cancer.[35, 36] Furthermore, the more sensitive the imaging technique, the less specific are the results.

In the absence of morphologic changes of definite CP on cross-sectional imaging, fibrosis has been documented in the pancreas on pathology (including autopsy) of longstanding alcohol use, smoking and multiple chronic diseases such as chronic kidney disease[37], liver cirrhosis[38], aging[39-41] and longstanding diabetes termed "pancreatopathy"[42] (Table 4).

Table 4. Examples of conditions where features of "fibrosis" are noted on imaging (endoscopic ultrasound) and/or pathology (autopsy) with no clinical history or symptoms of pancreatitis**.**

- Elderly
- Chronic alcohol use
- Chronic smoking
- Diabetes
- Chronic kidney disease
- Liver cirrhosis
- Intraductal Papillary Mucinous Neoplasm (IPMN)
- Pancreatic ductal adenocarcinoma (PDAC)
- Certain medications, e.g. cyclosporine

The significance of such findings in the absence of clinical symptoms is unclear and it is believed that these changes *do not* represent true CP. [43] In contrast to other chronic conditions of the Digestive system, such as inflammatory bowel disease or chronic liver disease, *histology* from the pancreas for a pathologic assessment is not typically available to evaluate the stage of disease or monitor its progress. Moreover, expert pathologists agree that fibrosis alone, even at more advanced stages may be non-specific and cannot be used to make a diagnosis of CP. [43] Likewise, pancreatic atrophy cannot be used to diagnose CP.[44]

Imaging features suggestive of CP in the absence of symptoms should be interpreted with caution in the elderly and in patients with alcohol or tobacco, diabetes mellitus, chronic kidney disease, liver cirrhosis, pancreatic neoplasia and certain drugs.

Fibrosis alone does not correlate with other features of CP.

Fibrosis, as well as other features that are characteristic of advanced CP such as exocrine pancreatic insufficiency (EPI), DM and chronic pain, do not develop at the same rate

in all patients – although they may eventually coexist in end-stage disease. For example, a cross sectional comparison of patients with CP in the North American Pancreatitis Study II (NAPS2) and others demonstrates a poor correlation between fibrosis and pancreatitis pain syndromes[45], EPI[46], pancreatic cancer risk[47] or clinical course when detected in the earlier disease phases.[19] This indicates that the progression of the CP syndrome represents semi-independent dysfunction and failure of the different specialized cell types and systems that contribute to pancreatic physiology and pathology.[11]

Fibrosis is a biomarker of pancreatic stellate cell activation and collagen deposition versus reabsorption. Other cell types may have different levels of activation and resilience to stress resulting in asynchronous progression from normal pancreas to end-stage CP.

Imaging changes suggestive of "Early CP" typically do not progress to CP.

The current approach is to use caution in making a definitive diagnosis of CP in the absence of obvious morphologic changes, especially since a disease is difficult to "undiagnose." The best way to make a confident diagnosis is longitudinal follow-up that confirms the presence of definitive changes associated with CP. As an example, during a median follow-up of 9 years at a tertiary care clinic, none of the 38 patients with chronic abdominal pain and 12 out of 38 (31.6%) diagnosed as "Early CP" based on EUS progressed to definite CP.[19] In another study that utilized EUS and pancreas function testing for diagnosis of CP, during an average follow-up of 7 years (IQR 3.5–9.5), 19 of 90 patients (21%) progressed to definite CP [14]. In Japan, a 2-year prospective study of 83 patients diagnosed with early CP noted that only 4 (4.8%) of patients progressed to CP, 48 (57.8%) remained unchanged and 31 (37.3%) improved or resolved[48] **Table 5** lists scenarios where Early CP is in the differential diagnosis.

Among these clinical scenarios, patients with prior AP or RAP have the highest risk of progressing to CP. In a systematic review of 14 studies, the probability of demonstrating features of CP on cross-sectional imaging during follow-up of at least one year was ~10% in patients with AP and ~36% in those with RAP[49]. The probability of prevalent CP or future progression to CP in each of the other clinical scenarios in Table 5 is much lower.

In most clinical cases, the imaging features suggestive of early CP will either resolve or fail to progress to CP. The group with highest risks are patient with AP and RAP, where rates of progression to CP may be 10% and 36%, respectively

Table 5. Clinical scenarios where CP is in the differential diagnosis, cross-sectional imaging does not show obvious changes of CP and other diagnoses have been excluded*

1. AP or RAP with or without chronic abdominal pain, exocrine and/or endocrine dysfunction
2. Unexplained chronic abdominal pain with normal or mild elevations in serum pancreatic enzymes
3. Vague upper abdominal symptoms, e.g. dyspepsia
4. Unexplained diarrhea with low fecal elastase-1 levels *and* equivocal or no response to pancreatic enzyme replacement therapy

*The likelihood of underlying CP varies based on the number and type of risk factors present (TIGAR-O List[3]). A confident diagnosis can only be established on longitudinal follow-up that confirms the presence of definitive changes of CP on cross-sectional imaging or histology.

Correlation between various biomarkers of CP is best at the extremes of the disease spectrum.

CP is a syndrome, indicating that several features must be present to make a diagnosis. As noted above, the classic triad of parenchymal calcifications, diabetes mellitus and steatorrhea capture the synergy of structural and functional abnormalities that only exist in true CP. These features collectively represent end-stage disease when there is little hope of reversal.

The clinical challenge is in identifying patients with true early CP, or evidence that the underlying pathogenic processes will progress to CP in the future. Clarity on the pathophysiology will require subdividing RAP and CP into groups of pathophysiologic mechanisms that can be independently measured and followed, and the development of new models of disease that consider external stressors and interaction between systems before individualized care is available.

Biomarkers of CP should be linked to specific cell types and processes, with correlation between clinical features of CP tracked on an individual basis.

Unmet needs for making a diagnosis of CP.

Clinical unmet needs for making an accurate and timely diagnosis of CP include:

a) Identifying prevalent CP in patients with suggestive symptoms but without sufficient imaging changes to make a confident clinical diagnosis.
b) Individualized prediction of disease progression and trajectory in those at-risk of or early established CP
c) Monitoring of disease activity and evaluating the effectiveness of interventions.

As noted in **Table 5**, in some clinical scenarios, CP is in the differential diagnosis. However, the lack of morphologic changes that meet the currently established criteria for CP diagnosis limits a clinician's ability to differentiate patients in whom a diagnosis of CP can be established or excluded with confidence. Making a confirmed diagnosis can allow a clinician to focus on management, while exclusion of diagnosis leads to consideration of other potential explanations for the patient's clinical presentation.

One concern of thought and opinion leaders for making diagnosis of Early CP in a lower-risk patient (e.g. chronic abdominal pain and normal or minimal changes of fibrosis on pancreatic imaging) is that the diagnosis of "CP" may trigger radical therapy, such as total pancreatectomy with islet autotransplantation (TPIAT).[1, 11] In contrast, doing "nothing" has a risk of the patient seeking treatment with another specialist who may embark on a therapeutic odyssey that leads to high cost and potential harm without significant benefit to the patient. We believe that the intensity of treatment be harmonized with the probability and certainty of diagnosis and stage, with reversible treatments (e.g. medications) takes precedence over irreversible treatments (e.g. surgical resections) unless otherwise required by clinical status.

Early treatment of "probable CP" should focus on minimizing recurrent pancreatitis, adopting a healthy lifestyle and using low-risk treatments targeting specific signs and symptoms.

In addition to clinical presentation, the *probability* of prevalent CP varies based on the presence of risk factors with different effect sizes. Representative examples are listed in **Table 6**.

Although the overall risk can be high in certain situations, most patients who have a risk factor will never develop CP (e.g. heavy alcohol use without a history of AP). In contrast, patients with multiple risk factors such as heavy alcohol consumption and/or smoking with one or more prior episodes of AP have a high risk of progression to CP. [51, 53]

Accurately predicting which patients will progress to definite CP has several advantages in patient management. In addition to regular follow-up, those identified to be at high-risk of progression would be candidates for risk factor modification and for emerging therapies such as those targeting chronic inflammation and preventing fibrosis when new treatments are available. In many cases of RAP, a primary underlying etiology can be identified that has targeted therapies to minimize further AP attacks.[53] High risk for diabetes mellitus should be managed with an endocrinologist to initiate optimal diet and minimize stressors (e.g. obesity). Celiac disease and AP / CP are diseases that overlap in a subset of patient.[54-56] The similarities of symptoms such as abdominal pain and maldigestion may confound early diagnosis and therefore treatment. Although pancreatitis increases the risk for pancreatic cancer, no effective screening program has been developed as in other high-risk groups.[57]

Given the heterogeneity of clinical presentation and course and, variability in the likelihood of CP among individuals with risk factors, having accurate biomarkers that can establish prevalent disease or predict future development of CP is needed. Biomarkers can include any combination of clinical symptoms, laboratory tests or imaging findings. There is no consensus regarding which biomarkers can accurately establish the diagnosis of Early CP or provide individualized prediction of disease progression.

Initiating preventative treatment based on probability of progression to pancreatitis or its complications is a future goal, awaiting evidence-based models and problem-based treatments.

Table 6. Risk of pancreatitis associated with select risk factors

Risk (%)*	Pancreatitis		Genetic risk factors		Heavy alcohol
	AP	RAP	PRSS1 (p.R122H or p>N21I)	Pancreas sufficient cystic fibrosis	
AP	20%	30-50%	80%	25%	6-8%
CP	10%	33%	40%	5-10%	4-5%
*Risk proportions shown are approximate. Presence of more than one risk factor will further increase the risk. Based on Oli[50], Sankaran[49], Takeyama [51] and Yadav[52]					

Mechanistic definition for CP

The Mechanistic Definition of CP proposed in 2016 and accepted by all major societies, [1, 11] provides a useful framework for developing strategies to diagnose CP with a *high probability* at an earlier stage, and to study its progression through the different stages of disease (see Tables 6 and 7). The Mechanistic Definition is linked to a progressive disease model driven by injury and inflammation that is triggered by an episode of AP to initiate the inflammatory process.[11] The key drivers are recurrent injury signaling, a pathogenic inflammatory response and/or failed regeneration of specialized cells.

Table 8. The five stages of a progressive model based on Mechanistic Definition of CP.

A) "At risk" (asymptomatic)
B) "Acute pancreatitis (initiates pancreatic inflammation)
C) "Early CP" (also called Suspected CP, and includes recurrent acute pancreatitis, RAP)
D) "Established CP" (defined by inflammation-related fibrosis and organ dysfunction)
E) "End Stage" (defined by loss of function and irreversible features)

Opportunities for progress.

One or more episodes of AP put the patient at high-risk of developing CP, with the likelihood of progression based on multiple risk factors. As a complex disorder, there is no "one size fits all" and personalized approaches are needed. It is also important to remember that at the time of initial presentation, as many as 40-50% of patients with CP may not have a prior history of AP.[58, 59] In contrast to older individuals, the rate of AP prior to CP is closer to 85%.[60]

The Mechanistic definition of CP is linked to a progressive model where the CP syndrome is broken down into 5 stages (**Table 8**).

In the context of early diagnosis of CP, the critical evaluation stage is C (Early CP / Suspected CP) which conceptually is characterized by a varying combination of (a) biomarkers of pancreatic injury and inflammation, (b) biomarkers of fibrosis, and (c) loss of organ function, depending on whether there is prevalent CP and the probability of future progression to CP. The type and number of risk factors in individual patients determine the likelihood of prevalent CP and future progression to CP. Patients with Established CP and End-stage CP will have biomarkers of fibrosis and variable biomarkers of injury and inflammation depending on the amount of ongoing inflammatory process.

The role of genetics in the etiologic diagnosis of CP.

Genetics is important to understanding the underlying mechanisms causing AP, CP and their complications. The challenge for physicians is that traditional medical school training focuses on classic Mendelian genetics that can be discovered by familial genetic studies where one pathogenic variant is a key gene (autosomal dominant as in hereditary pancreatitis) or two pathogenic variants on opposite gene alleles (autosomal recessive as in cystic fibrosis) cause a stereotypic disease syndrome in a high proportion of variant carriers. What three decades of genetic research in CP has taught us is that while numerous genetic variants are associated with RAP and CP, most of these are not sufficient nor necessary for development of pancreatitis, and many are common in the general population without detectable effects. Thus, a Precision Medicine model where the genetic factors are considered within mechanistic, engineering-based models, and where the integrated gene x environment predations are linked to clinical decision support information that is useful to the clinician. One example of practical implementation of the precision medicine concepts is the *SNaP-Shot™ Report* (Ariel Precision Medicine, Pittsburgh, PA) based on ~900,000 variants of known significance. Here, the characteristics of the patient are linked with the underlying genetic risk for different cell types and systems such as the Acinar Cell, Duct Cell, gallbladder disease (gallstone risk), dyslipidemia genes (hypertriglyceridemia risk), CP progression risk (linked to pathogenic immune processes), Type 2 diabetes risk (linked to T2DM polygenic risk score), and other predictors. This type of tool has the potential to provide any healthcare provider deep insights into the etiology of a disorder such as pancreatitis with clinical decision support advice in real time, at the point of care.[61]

New Precision Medicine tools are now available to assist in the diagnosis and management of specific aspects of pancreatitis and its complications. The effectiveness of these approaches compared to traditional management requires additional clinical studies.

Future Directions.

The primary challenge of diagnosing, evaluating and treating inflammatory disorders of the pancreas is the great heterogeneity of etiologies, severities, complications and trajectories. The use of genetic risk factors and broad biomarker discovery panels will be useful in linking pathogenic processes with detection and monitoring tools. This discovery process is further challenged by limited training and discipline in measuring and recording the patient's features. It is anticipated that ongoing work in the PROCEED study will help in developing biomarkers for the early diagnosis of CP and its progression.[62, 63]

References.

1. Whitcomb DC, Shimosegawa T, Chari ST, Forsmark CE, Frulloni L, Garg P, et al. 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. Pancreatology. 2018;S1424-3903(18):30113-3. PMID: 29793839

2. Yadav D, Slivka A. Managing chronic pancreatitis: the view from medical pancreatology. Am J Gastroenterol. 2018;113(8):1108-10. PMID: 29748562
3. Whitcomb DC, North American Pancreatitis Study G. Pancreatitis: TIGAR-O Version 2 Risk/Etiology Checklist With Topic Reviews, Updates, and Use Primers. Clin Transl Gastroenterol. 2019;10(6):e00027. PMID: 31166201
4. Fu D, Blobner BM, Greer PJ, Lafyatis R, Bellin MD, Whitcomb DC, et al. Pancreatitis-Associated PRSS1-PRSS2 Haplotype Alters T-Cell Receptor Beta (TRB) Repertoire More Strongly Than PRSS1 Expression. Gastroenterology. 2023;164(2):289-92 e4. PMID: 36191639
5. Whitcomb DC, Larusch J, Krasinskas AM, Klei L, Smith JP, Brand RE, et al. Common genetic variants in the CLDN2 and PRSS1-PRSS2 loci alter risk for alcohol-related and sporadic pancreatitis. Nature genetics. 2012;44(12):1349-54. PMID: 23143602
6. Dunbar E, Greer PJ, Melhem N, Alkaade S, Amann ST, Brand R, et al. Constant-severe pain in chronic pancreatitis is associated with genetic loci for major depression in the NAPS2 cohort. J Gastroenterol. 2020;55(10):1000-9. PMID: 32681239
7. Dunbar EK, Greer PJ, Amann ST, Alkaade S, Banks P, Brand R, et al. Pain Experience in Pancreatitis: Strong Association of Genetic Risk Loci for Anxiety and PTSD in Patients With Severe, Constant, and Constant-Severe Pain. Am J Gastroenterol. 2021;116(10):2128-36. PMID: 34236339
8. Ammann RW, Muellhaupt B. Progression of alcoholic acute to chronic pancreatitis. Gut. 1994;35:552-6. PMID: 8174996
9. Schneider A, Lohr JM, Singer MV. The M-ANNHEIM classification of chronic pancreatitis: introduction of a unifying classification system based on a review of previous classifications of the disease. J Gastroenterol. 2007;42(2):101-19. PMID: 17351799
10. Sun Y, Lu M, Feldman R, Saul M, Althouse A, Arteel G, et al. Positive Predictive Value of Cirrhosis and Chronic Pancreatitis Diagnoses in Individuals with Alcohol Use Disorder: A Single-Center Study. Dig Dis Sci. 2023. PMID: 38019381
11. Whitcomb DC, Frulloni L, Garg P, Greer JB, Schneider A, Yadav D, et al. Chronic pancreatitis: An international draft consensus proposal for a new mechanistic definition. Pancreatology. 2016;16:218-24. PMID: 26924663
12. Anaizi A, Hart PA, Conwell DL. Diagnosing Chronic Pancreatitis. Dig Dis Sci. 2017. PMID: 28315036
13. Sarner M, Cotton PB. Classification of pancreatitis. Gut. 1984;25(7):756-9. PMID: 6735257
14. Monachese M, Lee PJ, Harris K, Jang S, Bhatt A, Chahal P, et al. EUS and secretin endoscopic pancreatic function test predict evolution to overt structural changes of chronic pancreatitis in patients with nondiagnostic baseline imaging. Endosc Ultrasound. 2021;10(2):116-23. PMID: 33885007
15. DeWitt JM, Al-Haddad MA, Easler JJ, Sherman S, Slaven J, Gardner TB. EUS pancreatic function testing and dynamic pancreatic duct evaluation for the diagnosis of exocrine pancreatic insufficiency and chronic pancreatitis. Gastrointest Endosc. 2021;93(2):444-53. PMID: 32562609
16. Catalano MF, Sahai A, Levy M, Romagnuolo J, Wiersema M, Brugge W, et al. EUS-based criteria for the diagnosis of chronic pancreatitis: the Rosemont classification. Gastrointest Endosc. 2009;69(7):1251-61. PMID: 19243769
17. Vitali F, Zundler S, Jesper D, Wildner D, Strobel D, Frulloni L, et al. Diagnostic Endoscopic Ultrasound in Pancreatology: Focus on Normal Variants and Pancreatic Masses. Visc Med. 2023;39(5):121-30. PMID: 37899794
18. Mel Wilcox C, Gress T, Boermeester M, Masamune A, Levy P, Itoi T, et al. International consensus guidelines on the role of diagnostic endoscopic ultrasound in the management of chronic pancreatitis. Recommendations from the working group for the international consensus guidelines for chronic pancreatitis in collaboration with the International Association of Pancreatology, the American Pancreatic Association, the Japan Pancreas Society, and European Pancreatic Club. Pancreatology. 2020. PMID: 32631791
19. Sheel ARG, Baron RD, Sarantitis I, Ramesh J, Ghaneh P, Raraty MGT, et al. The diagnostic value of Rosemont and Japanese diagnostic criteria for 'indeterminate', 'suggestive', 'possible' and 'early' chronic pancreatitis. Pancreatology. 2018;18(7):774-84. PMID: 30119992
20. Ito K, Takasaki Y, Fujisawa T, Ishii S, Tomishima K, Takahashi S, et al. Current Situation and Problems in Diagnosis of Early Chronic Pancreatitis. Pancreas. 2023;52(5):e275-e81. PMID: 37782891
21. Frokjaer JB, Akisik F, Farooq A, Akpinar B, Dasyam A, Drewes AM, et al. Guidelines for the Diagnostic Cross Sectional Imaging and Severity Scoring of Chronic Pancreatitis. Pancreatology. 2018. PMID: 30177434
22. Tirkes T, Yadav D, Conwell DL, Territo PR, Zhao X, Venkatesh SK, et al. Magnetic resonance imaging as a non-invasive method for the assessment of pancreatic fibrosis (MINIMAP): a comprehensive study design from the consortium for the study of chronic pancreatitis, diabetes, and pancreatic cancer. Abdom Radiol (NY). 2019;44(8):2809-21. PMID: 31089778
23. Tirkes T, Shah ZK, Takahashi N, Grajo JR, Chang ST, Venkatesh SK, et al. Reporting Standards for Chronic Pancreatitis by Using CT, MRI, and MR Cholangiopancreatography: The Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer. Radiology. 2019;290(1):207-15. PMID: 30325281
24. Trikudanathan G, Walker SP, Munigala S, Spilseth B, Malli A, Han Y, et al. Diagnostic Performance of Contrast-Enhanced MRI With Secretin-Stimulated MRCP for Non-Calcific Chronic Pancreatitis: A Comparison With

Histopathology. Am J Gastroenterol. 2015;110(11):1598-606. PMID: 26372506
25. Stevens T, Dumot JA, Zuccaro G, Jr., Vargo JJ, Parsi MA, Lopez R, et al. Evaluation of duct-cell and acinar-cell function and endosonographic abnormalities in patients with suspected chronic pancreatitis. Clin Gastroenterol Hepatol. 2009;7(1):114-9. PMID: 18955165
26. Hart PA, Topazian M, Raimondo M, Cruz-Monserrate Z, Fisher WE, Lesinski GB, et al. Endoscopic Pancreas Fluid Collection: Methods and Relevance for Clinical Care and Translational Science. Am J Gastroenterol. 2016;111(9):1258-66. PMID: 27481304
27. Mehta DI, He Z, Bornstein J, Molle-Rios Z, Conwell DL, Horvath K. Report on the Short Endoscopic Exocrine Pancreatic Function Test in Children and Young Adults. Pancreas. 2020;49(5):642-9. PMID: 32433401
28. Lara LF, Takita M, Burdick JS, DeMarco DC, Pimentel RR, Erim T, et al. A study of the clinical utility of a 20-minute secretin-stimulated endoscopic pancreas function test and performance according to clinical variables. Gastrointest Endosc. 2017;86(6):1048-55 e2. PMID: 28385584
29. Conwell DL, Zuccaro G, Purich E, Fein S, Vargo JJ, Dumot JA, et al. Comparison of endoscopic ultrasound chronic pancreatitis criteria to the endoscopic secretin-stimulated pancreatic function test. Dig Dis Sci. 2007;52(5):1206-10. PMID: 17387611
30. Saad M, Vitale DS, Lin TK, Thapaliya S, Zhou Y, Zhang B, et al. Image or scope: Magnetic resonance imaging and endoscopic testing for exocrine and endocrine pancreatic insufficiency in children. Pancreatology. 2023;23(4):437-43. PMID: 37087303
31. Trikudanathan G, Vega-Peralta J, Malli A, Munigala S, Han Y, Bellin M, et al. Diagnostic Performance of Endoscopic Ultrasound (EUS) for Non-Calcific Chronic Pancreatitis (NCCP) Based on Histopathology. Am J Gastroenterol. 2016;111(4):568-74. PMID: 26952577
32. Rajan E, Clain JE, Levy MJ, Norton ID, Wang KK, Wiersema MJ, et al. Age-related changes in the pancreas identified by EUS: a prospective evaluation. Gastrointest Endosc. 2005;61(3):401-6. PMID: 15758911
33. Kong F, Pan Y, Wu D. Activation and Regulation of Pancreatic Stellate Cells in Chronic Pancreatic Fibrosis: A Potential Therapeutic Approach for Chronic Pancreatitis. Biomedicines. 2024;12(1). PMID: 38255213
34. Apte MV, Pirola RC, Wilson JS. Pancreatic stellate cells: a starring role in normal and diseased pancreas. Front Physiol. 2012;3:344. PMID: 22973234
35. Sarkar R, Xu Z, Perera CJ, Apte MV. Emerging role of pancreatic stellate cell-derived extracellular vesicles in pancreatic cancer. Semin Cancer Biol. 2023;93:114-22. PMID: 37225047
36. Zhang Z, Zhang H, Liu T, Chen T, Wang D, Tang D. Heterogeneous Pancreatic Stellate Cells Are Powerful Contributors to the Malignant Progression of Pancreatic Cancer. Front Cell Dev Biol. 2021;9:783617. PMID: 34988078
37. Avram MM. High prevalence of pancreatic disease in chronic renal failure. Nephron. 1977;18(1):68-71. PMID: 846627
38. Renner IG, Savage WT, 3rd, Stace NH, Pantoja JL, Schultheis WM, Peters RL. Pancreatitis associated with alcoholic liver disease. A review of 1022 autopsy cases. Dig Dis Sci. 1984;29(7):593-9. PMID: 6734367
39. Nagai H, Ohtsubo K. Pancreatic lithiasis in the aged. Its clinicopathology and pathogenesis. Gastroenterology. 1984;86(2):331-8. PMID: 6690361
40. Chantarojanasiri T, Hirooka Y, Ratanachu-Ek T, Kawashima H, Ohno E, Goto H. Evolution of pancreas in aging: degenerative variation or early changes of disease? J Med Ultrason (2001). 2015;42(2):177-83. PMID: 26576570
41. Stamm BH. Incidence and diagnostic significance of minor pathologic changes in the adult pancreas at autopsy: a systematic study of 112 autopsies in patients without known pancreatic disease. Human pathology. 1984;15(7):677-83. PMID: 6745910
42. Mohapatra S, Majumder S, Smyrk TC, Zhang L, Matveyenko A, Kudva YC, et al. Diabetes Mellitus Is Associated With an Exocrine Pancreatopathy: Conclusions From a Review of Literature. Pancreas. 2016. PMID: 26918874
43. Esposito I, Hruban RH, Verbeke C, Terris B, Zamboni G, Scarpa A, et al. Guidelines on the histopathology of chronic pancreatitis. Recommendations from the working group for the international consensus guidelines for chronic pancreatitis in collaboration with the International Association of Pancreatology, the American Pancreatic Association, the Japan Pancreas Society, and the European Pancreatic Club. Pancreatology. 2020;20(4):586-93. PMID: 32414657
44. Faghih M, Noe M, Mannan R, Kamel IR, Zaheer A, Kalyani RR, et al. Pancreatic volume does not correlate with histologic fibrosis in adult patients with recurrent acute and chronic pancreatitis. Pancreatology. 2020;20(6):1078-84. PMID: 32819846
45. Wilcox CM, Yadav D, Tian Y, Gardner TB, Gelrud A, Sandhu BS, et al. Chronic Pancreatitis Pain Pattern and Severity are Independent of Abdominal Imaging Findings. Clin Gastroenterol Hepatol. 2014;13(3):552-60. PMID: 25424572
46. Greer JB, Greer P, Sandhu BS, Alkaade S, Wilcox CM, Anderson MA, et al. Nutrition and Inflammatory Biomarkers in Chronic Pancreatitis Patients. Nutrition in clinical practice : official publication of the American Society for Parenteral and Enteral Nutrition. 2019;34(3):387-99. PMID: 30101991
47. Rebours V, Levy P, Mosnier JF, Scoazec JY, Soubeyrand MS, Flejou JF, et al. Pathology Analysis Reveals That Dysplastic Pancreatic Ductal Lesions Are Frequent in Patients With Hereditary Pancreatitis. Clin Gastroenterol Hepatol. 2009. PMID: 19765677

48. Masamune A, Nabeshima T, Kikuta K, Hamada S, Nakano E, Kume K, et al. Prospective study of early chronic pancreatitis diagnosed based on the Japanese diagnostic criteria. J Gastroenterol. 2019;54(10):928-35. PMID: 31270692
49. Sankaran SJ, Xiao AY, Wu LM, Windsor JA, Forsmark CE, Petrov MS. Frequency of progression from acute to chronic pancreatitis and risk factors: a meta-analysis. Gastroenterology. 2015;149(6):1490-500 e1. PMID: 26299411
50. Ooi CY, Dorfman R, Cipolli M, Gonska T, Castellani C, Keenan K, et al. Type of CFTR mutation determines risk of pancreatitis in patients with cystic fibrosis. Gastroenterology. 2011;140(1):153-61. PMID: 20923678
51. Takeyama Y. Long-term prognosis of acute pancreatitis in Japan. Clin Gastroenterol Hepatol. 2009;7(11 Suppl):S15-7. PMID: 19896091
52. Yadav D, Eigenbrodt ML, Briggs MJ, Williams DK, Wiseman EJ. Pancreatitis: prevalence and risk factors among male veterans in a detoxification program. Pancreas. 2007;34(4):390-8. PMID: 17446836
53. Whitcomb DC. Central role of the sentinel acute pancreatitis event (SAPE) model in understanding recurrent acute pancreatitis (RAP): Implications for precision medicine. Front Pediatr. 2022;10:941852. PMID: 36046477
54. Alkhayyat M, Saleh MA, Abureesh M, Khoudari G, Qapaja T, Mansoor E, et al. The Risk of Acute and Chronic Pancreatitis in Celiac Disease. Dig Dis Sci. 2020. PMID: 32809104
55. Sadr-Azodi O, Sanders DS, Murray JA, Ludvigsson JF. Patients with celiac disease have an increased risk for pancreatitis. Clin Gastroenterol Hepatol. 2012;10(10):1136-42 e3. PMID: 22801059
56. Ludvigsson JF, Montgomery SM, Ekbom A. Risk of pancreatitis in 14,000 individuals with celiac disease. Clin Gastroenterol Hepatol. 2007;5(11):1347-53. PMID: 17702659
57. Dbouk M, Katona BW, Brand RE, Chak A, Syngal S, Farrell JJ, et al. The Multicenter Cancer of Pancreas Screening Study: Impact on Stage and Survival. J Clin Oncol. 2022;40(28):3257-66. PMID: 35704792
58. Hori Y, Vege SS, Chari ST, Gleeson FC, Levy MJ, Pearson RK, et al. Classic chronic pancreatitis is associated with prior acute pancreatitis in only 50% of patients in a large single-institution study. Pancreatology. 2019;19(2):224-9. PMID: 30795927
59. Cook ME, Bruun NH, Davidsen L, Drewes AM, Olesen SS. Multistate Model of the Natural History of Inflammatory Pancreatic Diseases: A Nationwide Population-based Cohort Study. Gastroenterology. 2023;165(6):1547-57 e4. PMID: 37659669
60. Kumar S, Ooi CY, Werlin S, Abu-El-Haija M, Barth B, Bellin MD, et al. Risk Factors Associated With Pediatric Acute Recurrent and Chronic Pancreatitis: Lessons From INSPPIRE. JAMA Pediatr. 2016;170(6):562-9. PMID: 27064572
61. Kohane IS. HEALTH CARE POLICY. Ten things we have to do to achieve precision medicine. Science. 2015;349(6243):37-8. PMID: 26138968
62. Yadav D, Park WG, Fogel EL, Li L, Chari ST, Feng Z, et al. PROspective Evaluation of Chronic Pancreatitis for EpidEmiologic and Translational StuDies: Rationale and Study Design for PROCEED From the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer. Pancreas. 2018;47(10):1229-38. PMID: 30325862
63. Jeon C, Hart PA, Li L, Yang Y, Chang E, Bellin MD, et al. Development of a Clinical Prediction Model for Diabetes in Chronic Pancreatitis: The PREDICT3c Study. Diabetes Care. 2022. PMID: 36382801

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Conflicts of Interest

DCW is a cofounder and consultants to Ariel Precision Medicine., He serves as CSO and Chair, Medical Advisory Board at Ariel Precision Medicine and has equity,

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