Idiopathic recurrent acute pancreatitis: current and future approaches to management

Pranjal Singh, Soumya Jagannath Mahapatra and Pramod Kumar Garg

Purpose of review
Idiopathic recurrent acute pancreatitis (IRAP) is a clinically relevant condition with a high likelihood of progression to chronic pancreatitis (CP) in 20–50% of patients. This review outlines the importance of early diagnosis of IRAP and potential upcoming therapies to halt disease progression. It highlights a potential therapeutic window in the natural history of IRAP.

Recent findings
Despite advancements in diagnostic modalities, identifying a definitive aetiology remains challenging in a significant proportion of cases. Current approaches emphasize structured, stepwise evaluation including metabolic, genetic, and structural factors. Emerging therapies aim to target inflammation, trypsin activation, and pancreatic fibrosis.

Summary
While diagnostic tools have improved, therapeutic options remain limited in IRAP. Early identification of modifiable risk factors, use of advanced imaging, and application of evolving treatment strategies may offer an opportunity to prevent the transition from IRAP to CP. Future research must focus on validating disease-modifying treatments and optimizing individualized management strategies.

Keywords
chronic pancreatitis, endoscopic ultrasound, fibrosis, idiopathic recurrent acute pancreatitis, therapeutic window

INTRODUCTION

Recurrent acute pancreatitis (RAP) is defined as "a syndrome of multiple distinct acute inflammatory episodes involving the pancreas in individuals with genetic, environmental, metabolic, biologic, and/or other risk factors, who experienced two or more episodes of acute pancreatitis, separated by at least 3 months" [1]. A three-month time has been arbitrarily taken to demonstrate the resolution of pancreatitis between two episodes. Patients with AP who develop local complications may have pain and elevated amylase during recovery and should be differentiated from RAP.

RAP has an estimated annual incidence of 8–10 per 100 000 and prevalence of 110–140 per 100 000) [2▪]. Most common aetiologies are alcohol and gallstones which are treatable causes while 10–26.8% are idiopathic [3–5]. Despite advancement in the diagnostic modalities, the incidence of "idiopathic RAP" has not decreased. In a systematic review, the recurrence rate following a first attack of acute pancreatitis (AP) was estimated at around 20%, with the risk of progression from RAP to CP reaching approximately 35% [6▪] (Fig. 1). The recurrence rates are higher with a predilection to develop CP in up to 20–50% [7▪,8,9▪] in patients with idiopathic RAP.

Understanding the pathophysiological mechanisms, optimizing diagnostic algorithms, and developing targeted therapies early in the disease course are crucial for improving outcomes in these patients. Idiopathic recurrent acute pancreatitis (IRAP) should not be viewed as a benign or self-limited condition. Rather, it represents an early phase in the natural history of chronic pancreatitis (CP), offering a unique surveillance and therapeutic window for disease-modifying interventions. This review aims to provide a comprehensive overview of current practices in diagnosing and managing RAP, as well as explore emerging advancements in the field.

Department of Gastroenterology and Human Nutrition, All India Institute of Medical Sciences, New Delhi, India

Correspondence to Soumya Jagannath Mahapatra, MD, DM Room No. 3111, Department of Gastroenterology, All India Institute of Medical Sciences, New Delhi 110029, India.
E-mail: soumyajagannath@yahoo.com

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KEY POINTS

- Idiopathic recurrent acute pancreatitis (IRAP) carries a significant risk of progression to chronic pancreatitis in 20–50% of patients.
- Endoscopic ultrasound and MRI may be helpful in ruling out microlithiasis, small ampullary tumour and congenital anomalies such as pancreas divisum.
- Approximately 40–50% patients have associated genetic mutation in SPINK1, CFTR, PRSS1, CTRC and CPA1 gene. Genetic testing may be considered in select patients but offers limited therapeutic benefit in routine clinical practice.
- Novel therapies targeting trypsin activation, interleukin-6 signalling, and pancreatic fibrosis are under early investigation.
- Timely intervention during the therapeutic window in IRAP may help prevent long-term pancreatic damage and progression to chronic disease.

NATURAL HISTORY OF IDIOPATHIC RECURRENT ACUTE PANCREATITIS

Progression from a structurally normal pancreas to CP has been reported in approximately 4% to 36% of patients with RAP [10–12,13▪▪,14]. A meta-analysis showed that 10% of patients with first episode of AP develop RAP and 36% of individuals with RAP eventually developed chronic disease [6▪], and that patients with RAP had a threefold increased risk of progression to CP compared to those with only a single episode of acute pancreatitis (AP) [15] (Fig. 2).

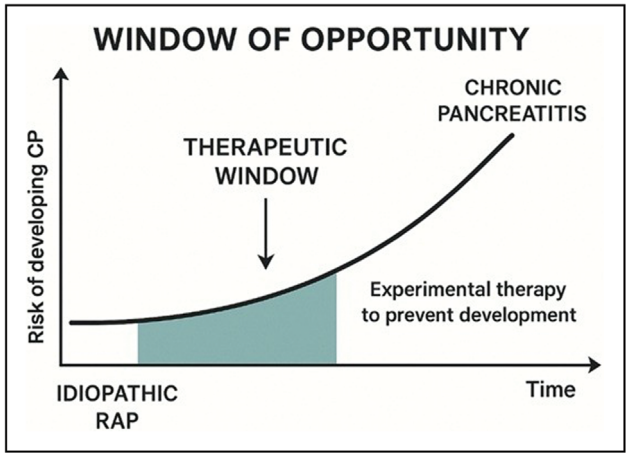

FIGURE 1. Concept of "therapeutic window" in the RAP to CP progression. CP, chronic pancreatitis; RAP, recurrent acute pancreatitis.

A comprehensive meta-analysis involving 17 849 patients across 36 studies found a 21% recurrence rate following a first episode of AP [16]. Subgroup analysis by aetiology revealed recurrence risks of 14% for gallstone-induced, 30% for alcohol-related and hyperlipidaemia-induced, and 25% for idiopathic pancreatitis. Treating the underlying cause markedly reduced recurrence – from 14% to 4% in biliary and 30% to 6% in alcohol-induced pancreatitis [17]. In another study, recurrent pancreatitis developed in 12% with biliary, 24% with alcoholic and 25% with idiopathic AP. Over a median follow-up of 58 months, CP occurred in 3%, 16%, and 10% following biliary, alcohol, and idiopathic AP [18▪▪].

The severity of recurrent episodes of pancreatitis are usually mild, though the sentinel episode might be severe. Severe first episode has higher risk of progression to CP especially in alcoholics [13▪▪,14].

ETIOLOGICAL EVALUATION OF IDIOPATHIC RECURRENT ACUTE PANCREATITIS

After alcohol and gallstones have been ruled out, patients with RAP need evaluation before they are labelled as nAnB IRAP (nonalcoholic nonbiliary IRAP) [1].

MICROLITHIASIS

Microliths have been defined as gallstones <3 mm in size. A cut-off of 3 mm has been chosen as transabdominal ultrasound (USG) can detect gallstones >3 mm in size. Recent study differentiate between biliary sludge as hyperechoic material without acoustic shadowing and microlith as echo rich calculus of ≤ 5 mm with acoustic shadowing [19]. Studies have shown that up to 92% of patients initially suspected to have microlithiasis developed detectable gallstones on follow-up USG [20], and 75% progressed to gallstone formation in another cohort [21]. Endoscopic ultrasound (EUS) remains the most sensitive modality, detecting microliths in up to 96% of cases [22].

The reported prevalence of microlithiasis in IRAP ranges between 10% and 13% [9▪,23]. It should be considered a likely aetiology only if liver enzymes are elevated within 24–48 h of symptom onset, mimicking biliary pancreatitis. Ross *et al.* described that patients with cholesterol crystals on bile microscopy often formed gallstones within 6 months, supporting a cause-effect relationship. Conversely, lack of gallstone formation over this period makes microlithiasis an unlikely contributor [20]. There is no role of empirical cholecystectomy in the absence of stone or microlith in patients with IRAP.

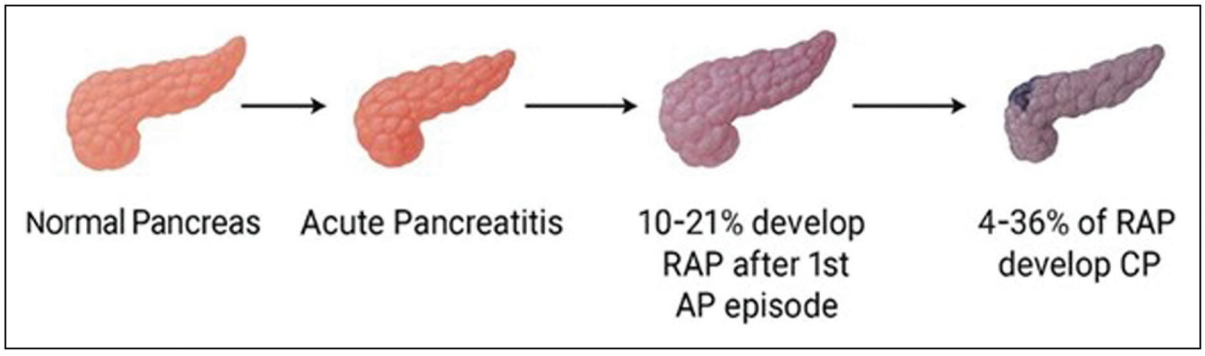

FIGURE 2. Natural history after the first attack of acute pancreatitis.

PANCREATIC DIVISUM

Pancreatic divisum (PD) is the most common congenital anomaly of the pancreas, occurring in 5–14% of the general population, including the Indian population [24]. Its role in pathogenesis of RAP remains controversial. Some argue that PD contributes to RAP by causing functional obstruction of pancreatic secretions due to inadequate drainage through the minor papilla. The proponents suggest that the frequency of PD is much higher in patients with IRAP than that in the general population. Gonoi *et al.* recently demonstrated a significantly higher prevalence of PD among patients with IRAP, reporting a rate of 33% compared to just 2.6% in healthy individuals [25]. However, the pathogenic role of PD remains debated. Critics highlight that PD is often an incidental, asymptomatic finding in the general population [20], and clinical response to endoscopic therapy such as minor papilla sphincterotomy is inconsistent and frequently suboptimal. Recent results of SHARP trial show no benefit of minor papilla sphincterotomy to prevent recurrence of pancreatitis [26▪].

Genetic mutations especially *SPINK1* and *CFTR* gene have been shown to be associated with PD and RAP. A study showed no increased prevalence of PD in IRAP compared to healthy controls or alcohol-related pancreatitis patients but the PD prevalence was significantly higher in patients with CFTR mutations [27–28]. These findings suggest that PD alone is not sufficient to cause RAP, but when combined with genetic susceptibility, it may increase the risk of disease progression.

SPHINCTER OF ODDI DYSFUNCTION

Sphincter of Oddi dysfunction (SOD) was previously thought to be responsible for 35–65% of recurrent acute pancreatitis [29–33] cases. SOD is characterized by increased basal sphincter pressure, affecting the biliary, pancreatic, or both segments [34]. Higher basal sphincter pressure gradients between the common bile duct (CBD) and duodenum suggest a potential role of sphincter dysfunction in RAP.

Types of SOD:

(1) Type 1 SOD: Also known as papillary stenosis leads to persistent biliary/pancreatic duct obstruction.
(2) Type 2 SOD: The diagnosis requires documentation of sphincter dysfunction and its clinical significance is uncertain.
(3) Type 3 SOD: It has now been reclassified as functional pain under the Rome IV consensus.

In patients with SOD1 endoscopic sphincterotomy (ES) should be considered. However, abnormal manometry did not translate into clinical improvement after ES [35]. The role of ES is controversial in Type 2 SOD. In a randomized controlled trial, biliary sphincterotomy was equally effective as dual biliary and pancreatic sphincterotomy [7▪]. There is no benefit from sphincterotomy in Type 3 SOD as shown in the EPISOD trial [36▪▪].

ABNORMAL BILIO-PANCREATIC DUCT UNION

Abnormal bilio-pancreatic duct union (ABPDU) is present in 1.5%–3% of healthy individuals [37]. In ABPDU, there is anomalous union of the pancreatic and bile ducts outside the duodenal wall with a long common channel $\geq$15 mm. This may lead to reflux of bile into the pancreatic duct leading to acute pancreatitis.

ANNULAR PANCREAS

Annular pancreas is a congenital anomaly due to failure of rotation of the ventral bud. This results in a band of pancreatic tissue encircling the second part of the duodenum. It may cause duodenal obstruction particularly when it is complete in children. It has been considered as a cause of RAP but the association is weak.

CHOLEDOCHOCELE

There is cystic dilatation of lower end of bile duct which may cause obstruction to pancreatic flow. The treatment involves endoscopic sphincterotomy and deroofing.

PANCREATICOBILIARY TUMOURS

Pancreatic tumours can present as recurrent acute pancreatitis, especially in older patients (>50 years). Despite advances in imaging, smaller lesions may be missed by cross-sectional imaging (CT scan or MRI). Endoscopic ultrasound has a high sensitivity for the detection of small lesions (<2 cm), and hence is recommended for evaluation of unexplained pancreatitis, especially in patients aged 50 years or older [38].

METABOLIC FACTORS

HTG, especially when serum triglyceride levels exceed 1000 mg/dl, is a recognized cause of both AP and RAP. It contributes to 1–7% of pancreatitis cases [39]. Genetic predisposition may amplify risk; a study involving 126 HTG patients found that 10.3% carried CFTR mutations, and the mutation was more prevalent in patients who developed pancreatitis (26.1% vs. 1.3%; $P < 0.0001$) [40].

Recent studies have shown that newer therapies with an antisense oligonucleotide targeting messenger RNA for apolipoprotein C-III (APOC3), such as volanesorsen and olezarsen have been shown to reduce the recurrence of pancreatitis which is concomitant with reduction in triglyceride levels [41▪▪,42▪▪]. Although rare, hypercalcemia is a treatable metabolic cause of RAP. Importantly, calcium levels may be spuriously normal during an acute attack, so measurement in the quiescent phase is essential. Workup includes serum PTH levels and neck ultrasound, and if needed, a Tc-99m sestamibi scan to localize parathyroid adenomas.

GENETIC FACTORS IN RECURRENT ACUTE PANCREATITIS

Inheritance patterns

RAP may follow various genetic inheritance patterns. The most recognized is autosomal dominant inheritance, often linked to gain-of-function mutations in the *PRSS1* gene on chromosome 7q35 [43]. This gene encodes cationic trypsinogen (trypsin-1), a precursor of the digestive enzyme trypsin. Around 10% of Western Caucasian children with RAP carry a pathogenic *PRSS1* variant [44,45].

Variants in *SPINK1*, which encodes a pancreatic trypsin inhibitor, are also implicated in RAP and CP. Both homozygous and heterozygous mutations may predispose to disease, though the latter often act as modifiers, increasing susceptibility when combined with other risk factors [46].

Additional genes involved include *CFTR, CTRC, CPA1* and *CLDN2/MORC4*, which regulate pancreatic enzyme activity and stress responses [47▪▪].

The common molecular mechanism involves dysregulated trypsin activation. Premature conversion of trypsinogen to trypsin within the pancreas leads to autodigestion and inflammation. Normally, protective mechanisms like trypsin inhibition exist, but mutations in genes such as *SPINK1* and *CTRC* may impair these defences [48].

WHEN TO OFFER GENETIC TESTING?

Genetic testing may be offered to the following subset of patients.

(1) First episode of idiopathic acute pancreatitis if:
   (a) Age <18 years
   (b) Family history of pancreatitis
(2) Idiopathic recurrent AP

However, routine genetic testing may cause unnecessary psychological burden on the patients without giving the advantage of any therapeutic benefit as of now. Genetic testing may help avoid unnecessary investigations for the etiological workup. The option of genetic testing should be discussed with the patient and family before it is ordered.

DIAGNOSTIC APPROACH TO NONALCOHOLIC, NONBILIARY IDIOPATHIC RECURRENT ACUTE PANCREATITIS

A comprehensive clinical assessment is crucial in evaluating patients with nonalcoholic, nonbiliary idiopathic recurrent acute pancreatitis (nAnB IRAP). This starts with a detailed history and physical exam, focusing on medication use, alcohol and tobacco consumption, and family history of pancreatic or lipid metabolism disorders, including congenital hyperlipidemia. Investigations are typically organized into three phases (Table 1).

PHASE 1 INVESTIGATIONS

Routine serum chemistries should include serum calcium and fasting triglyceride levels. While TG may be transiently elevated in alcoholic pancreatitis, a level >1000 mg/dl supports hypertriglyceridemia as the cause. These tests should be repeated once the acute episode resolves.

Table 1. Level of investigations in a case of recurrent acute pancreatitis

Level I	Level II	Level III
Serum calcium	EUS	Sweat chloride level (young patients)
Fasting lipids (triglycerides)	MRCP	Genetic mutational analysis (*PRSS1, SPINK 1, CFTR, CTRC, CPA1*)
Liver function tests (ALT) within 48 h of AP		
Trans-abdominal USG abdomen		
CECT scan of the abdomen		

Liver function tests (LFTs) are key for diagnosing biliary causes, even if transabdominal ultrasound is negative for gallstones. ALT >3× ULN and bilirubin >3 mg/dl, which normalize within 2–3 days, strongly suggest a biliary aetiology. An ALT >150 IU/l has shown 96% sensitivity for biliary pancreatitis [49].

If aetiology remains unclear after Phase 1, the diagnosis is nAnB IRAP, and Phase 2 investigations are warranted.

Imaging: A repeat abdominal ultrasound after recovery (usually at 3 months) may detect gallstones missed initially. CECT can help identify pancreatic calcifications, ductal dilatation, tumours, or complications of RAP.

PHASE II INVESTIGATIONS ENDOSCOPIC ULTRASOUND

It has now become the investigation of choice in nAnB IRAP, particularly effective in detecting microlithiasis, small neoplasms, congenital anomalies, and early CP. It has high sensitivity (up to 96%) for microliths and a negative predictive value of 95.4% for common bile duct stones [50]. EUS also outperforms other modalities in identifying small periampullary tumours. In RAP without overt chronicity on CT or MRCP, EUS is valuable in diagnosing early CP.

For optimal results, EUS should be delayed 6–8 weeks after mild to moderate acute pancreatitis to avoid confounding inflammation. If peripancreatic collections are present, EUS should be postponed until resolution.

ERCP has no diagnostic role; its use is limited to therapeutic indications such as choledocholithiasis or choledochocoele [51].

MRCP is a noninvasive tool for imaging the biliary and pancreatic ducts. It can detect neoplasms, congenital anomalies like pancreas divisum, and bile duct stones. Secretin-enhanced MRCP (S-MRCP) improves ductal visualization, aiding early CP and pancreas divisum diagnosis with superior sensitivity over standard MRCP [52]. Both EUS and MRCP are often required to evaluate the aetiology and assess for CP.

Phase III investigations: Genetic testing may be considered in those with a family history or subtle CP features, though its clinical utility is limited. Sweat chloride testing is done when cystic fibrosis is suspected. Serum autoantibodies are generally not helpful; autoimmune pancreatitis is pathophysiologically and clinically distinct from IRAP and should not be routinely screened with IgG4.

FUTURE DIRECTIONS IN NONALCOHOLIC, NONBILIARY IDIOPATHIC RECURRENT ACUTE PANCREATITIS DIAGNOSIS AND MANAGEMENT

RAP remains a significant clinical challenge, often progressing to CP. Emerging research should focus on novel diagnostic and therapeutic strategies, including artificial intelligence (AI), inflammatory biomarkers, epigenetics, and targeted therapies.

EMERGING THERAPIES IN RECURRENT ACUTE PANCREATITIS AND EARLY CHRONIC PANCREATITIS

Targeting inflammation and acinar cell injury

Rationale

The early stages of RAP and CP are driven by repetitive acinar cell injury, intra-acinar activation of trypsinogen, and an amplified inflammatory cascade [53]. These mechanisms contribute to sustained immune activation and predispose to progressive fibrosis, if unchecked.

Emerging therapies

A. Trypsin inhibitors

Camostat mesylate: It is a serine protease inhibitor that blocks intrapancreatic trypsinogen activation. Studies from Japan demonstrate its efficacy in alleviating pain and slowing progression in early CP [54]. However, a recent phase II randomized controlled

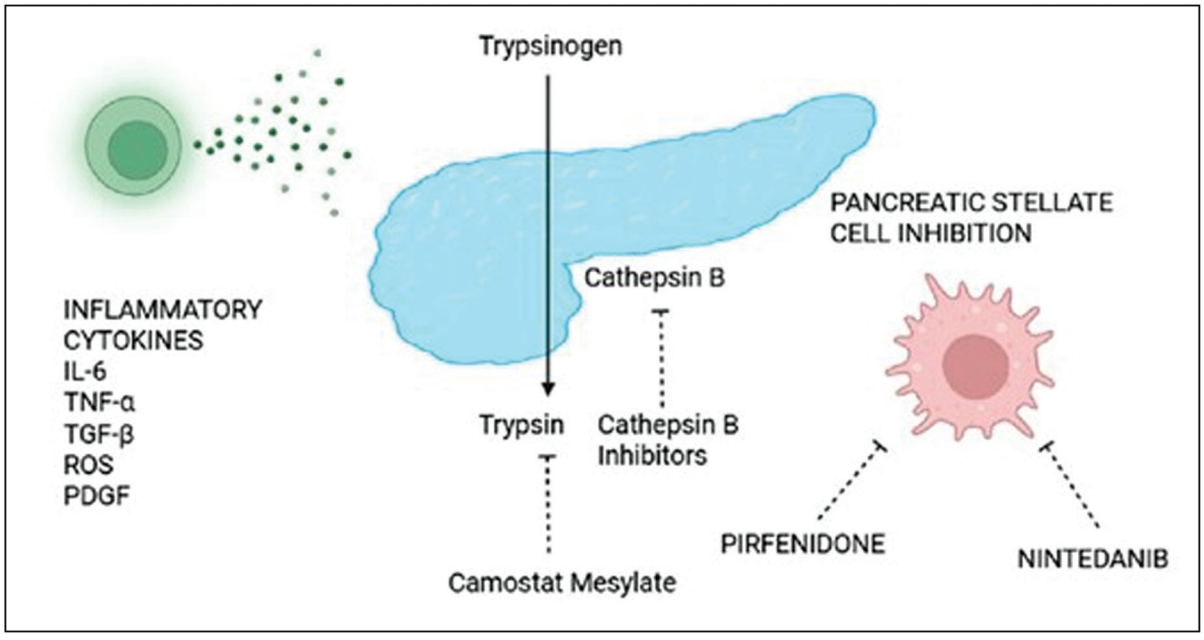

FIGURE 3. Newer therapies during the window period in managing RAP and early CP. Nintedanib and pirfenidone are antifibrotic agents that target the pancreatic stellate cells. Camostat mesylate is an oral trypsin inhibitor. CP, chronic pancreatitis; RAP, recurrent acute pancreatitis.

trial did not show improvement in pain score in patients with chronic pancreatitis [55▪].

B. Cathepsin B inhibitors

Cathepsin B mediates pathological trypsinogen activation. Knockout studies in mice have shown protection from pancreatitis but there are no studies in humans [56].

C. Interleukin-6 inhibition

Interleukin-6 (IL-6) has been implicated as a key mediator of inflammation in AP [57]. Some authors have shown its importance in RAP and CP also [58]. A randomized trial is ongoing in Denmark to show the benefit of IL-6 inhibition by Tocilizumab to prevent frequent episodes in IRAP [59].

Targeting pancreatic stellate cells and fibrogenesis

Rationale

Pancreatic stellate cells are key mediators of fibrosis in CP. Repeated injury and inflammation stimulate PSC activation, leading to excessive extracellular matrix (ECM) production. Targeting PSCs offers a potential to reverse or prevent fibrosis (Fig. 3).

Emerging therapies

(1) Pirfenidone: It is an antifibrotic agent approved for idiopathic pulmonary fibrosis. It suppresses TGF-β1 and collagen production in activated PSCs. Preclinical studies demonstrate reduced fibrosis in experimental models of CP [60].

(2) Nintedanib: It is a tyrosine kinase inhibitor used in pulmonary fibrosis. It has shown potential in suppressing PSC activation and ECM deposition in early experimental pancreatitis [61].

(3) Vitamin A-coupled siRNA Nanoparticles (VA-lipsiRNAgp46): It is a novel delivery system targeting gp46, a chaperone protein critical for collagen secretion in PSCs. Vitamin A allows selective uptake by PSCs. In a rat model, this therapy significantly reduced fibrosis and stellate cell activation [62].

CONCLUSION

IRAP represents a distinct disease entity with high chance to progression to CP. Effective management of patients with RAP involves early identification of risk factors such as genetic mutation, metabolic abnormalities and occult tumours, along with timely intervention to prevent progression to chronic pancreatitis. Targeting acinar injury and fibrogenesis within the therapeutic window, emerging therapies like trypsin and stellate cell inhibitors offer promising disease-modifying potential. Multidisciplinary care and personalized treatment strategies are key to optimizing long-term outcomes.

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Conflicts of interest

There are no conflicts of interest.

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