

# Chronic pancreatitis

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Chronic pancreatitis is a multifactorial, fibroinflammatory syndrome in which repetitive episodes of pancreatic inflammation lead to extensive fibrotic tissue replacement, resulting in chronic pain, exocrine and endocrine pancreatic insufficiency, reduced quality of life, and a shorter life expectancy. The incidence and prevalence of chronic pancreatitis is rising and no curative treatment is available. Using novel diagnostic algorithms, definitive chronic pancreatitis can be diagnosed by imaging criteria alone, whereas probable chronic pancreatitis requires clinical features and imaging criteria. Criteria for the diagnosis of early chronic pancreatitis are still under discussion and need prospective validation in clinical trials. Cross-sectional imaging should be used first; endoscopic ultrasound is needed only when CT or MRI are inconclusive or to plan therapeutic interventions. Management of chronic pancreatitis requires an interdisciplinary approach including primary care practitioners, gastroenterologists, surgeons, radiologists, pain specialists, and nutritional therapists. Patients with chronic pancreatitis should be seen at least once a year and re-evaluated for causal risk factors, symptom control, and complications such as malnutrition, pancreatic exocrine insufficiency, and diabetes; refer to a specialised centre if symptoms are poorly controlled or there is risk of deterioration. Scoring systems to monitor disease progression have been developed and validated internationally. Interventional treatments for pain or cholestasis should be done by specialists only, and early discussion of treatment approaches should include all medical disciplines involved in care. Throughout this Seminar, we address research needs such as staging of pancreatitis, aspects of malnutrition and pain, and cancer surveillance, to help improve the care of patients.

## Definition of chronic pancreatitis

The term chronic pancreatitis is commonly used to describe a fibroinflammatory syndrome of the exocrine pancreas, in which repetitive episodes of pancreatic inflammation of variable intensity and length lead to irreversible pancreatic tissue damage.<sup>1,2</sup> Although several causes of chronic pancreatitis have been described in the literature (the latest being autoimmune pancreatitis), some of which differ in their natural history, most patients will develop typical clinical and morphological features. Signs of definitive chronic pancreatitis are parenchymal or intraductal calcifications, pancreatic fibrosis, exocrine and endocrine pancreatic insufficiency resulting in malabsorption and diabetes, pain, and an increased risk of pancreatic cancer. Quality of life (QOL) and life expectancy are also reduced.

Although alcohol and tobacco use are the most prevalent risk factors among adult patients with chronic pancreatitis, we now understand that it is rare for a single risk factor, rather than multiple susceptibilities, to cause chronic pancreatitis. A draft mechanistic definition of chronic pancreatitis therefore included a step-wise progression model, in which some individuals considered to be at risk, undergoing one or recurrent episodes of pancreatic inflammation, will develop irreversible damage. Whether this concept truly fits the natural history and, more importantly, whether it can be applied to patient care in clinical practice, needs to be tested in prospective observational studies. To design suitable trials, novel biomarkers (including sensitive imaging techniques) are needed that can detect early changes and distinguish pancreatitis from other diseases. In line with these considerations, another discussion is ongoing: previous definitions have used definitive stages of chronic pancreatitis as a conceptual starting point and worked their way backwards. In contrast, the international consensus statements on early chronic

pancreatitis developed by members of the International Association of Pancreatology, American Pancreatic Association, Japan Pancreas Society and and European Pancreatic Club have suggested criteria that define early, possible, and definitive chronic pancreatitis (table 1, panel).<sup>4</sup> The consensus statements also include a list of factors meant to increase or decrease the likelihood of finding chronic pancreatitis, allowing trialists to enrich cohorts and to exclude individuals at very low risk of developing chronic pancreatitis during follow-up.

## How does typical chronic pancreatitis differ from other inflammatory diseases of the pancreas?

Acute and recurrent acute pancreatitis are defined by the full recovery of the organ.<sup>9</sup> However, in necrotising pancreatitis, the loss of pancreatic parenchyma can sometimes not be compensated by the remaining tissue, and pancreatic insufficiency develops but other features of chronic pancreatitis are missing. Pancreatic fibrosis can also occur in other conditions, most prominently because of desmoplastic stroma reaction in pancreatic cancer, increasing age, or diabetes, and should not be confused

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### Search strategy and selection criteria

Data for this Seminar were identified by searches of MEDLINE, Current Contents, PubMed, and the references from relevant articles using the search terms "chronic pancreatitis".

Only articles published in English or German between Jan 1, 2014, and Dec 31, 2019, with full text available were included. Additionally, abstracts and reports from United European Gastroenterology Week 2018 and 2019 were searched manually. Literature was updated manually in April, 2020, during the revision process for this Seminar.

	Definitive chronic pancreatitis	Probable chronic pancreatitis	Early or suggestive chronic pancreatitis (consensus only)
Diagnostic method	Clinical features and probable imaging criteria, or definitive imaging criteria alone	Clinical features and probable imaging criteria	Clinical features, with or without presence of risk factors, and suggestive imaging criteria
Clinical features	Two or more of the following clinical features: repeated upper abdominal pain; abnormal serum or urine pancreatic enzyme concentrations (lipase or amylase activity 2–3 times above the upper limit of normal); abnormal exocrine function (stool elastase less than 200 µg/g)	Two or more of the following clinical features: repeated upper abdominal pain; abnormal serum or urine pancreatic enzyme concentrations (ie, lipase or amylase activity 2–3 times above the upper limit of normal); abnormal exocrine function (stool elastase <200 µg/g)	Three or more of the following clinical features, and other likely causes excluded: repeated upper abdominal pain; abnormal serum or urine pancreatic enzyme concentrations; abnormal exocrine function; continuous heavy alcohol consumption (>80 g/day), or pedigree of hereditary chronic pancreatitis, or known sporadic high-risk mutation
Imaging criteria <sup>3</sup>	Definitive imaging criteria according to Cambridge classification (Cambridge Grade 4)	Probable imaging criteria according to Cambridge classification (Cambridge Grade 3)	Probable imaging criteria according to Cambridge classification (Cambridge Grade 2)
Endoscopic retrograde cholangiopancreatography	Grade 3 plus at least one of pseudocyst ≤10 mm, pancreatic duct stones, main duct strictures, or extension to neighbouring organs	Grade 2 plus irregular main pancreatic duct	More than three pathological side branches plus normal main pancreatic duct
Ultrasound	Grade 3 plus at least one of pancreatic duct stones, main duct obstruction, inflammatory mass >×2, or splenic vein thrombosis	Grade 2 plus cysts or focal calcifications	Irregular main pancreatic duct >3 mm, hyperechoic pancreatic duct wall, or lobularity with stranding
CT or MRI	Grade 2 or Grade 3 plus at least one of pseudocyst ≥10 mm parenchymal calcifications, main duct calcifications, main duct obstruction, or main duct irregularities	All of Grade 2 criteria plus pathological main pancreatic duct with dilatation >4 mm	Two or more of the following criteria: main pancreatic duct 2–4 mm; mild organ enlargement; heterogeneous parenchyma; pseudocysts ≤10 mm; irregular main pancreatic duct ≥ three pathological side branches

Criteria adopted from Hoffmeister and colleagues (2015),<sup>1</sup> Whitcomb and colleagues (2018),<sup>4</sup> Ito and colleagues (2016),<sup>5</sup> and Löhr and colleagues (2017).<sup>6</sup>

**Table 1: Diagnostic criteria for chronic pancreatitis**

with chronic pancreatitis. Whether minimal change pancreatitis and pancreatic atrophy are stages during disease development from early to late chronic pancreatitis, or separate clinical entities, is still under debate. Autoimmune pancreatitis is a unique entity that shares some features with chronic pancreatitis, because it can present as chronic inflammation of the pancreas and lead to similar end stages. However, some striking features set it apart from other forms of pancreatitis: first, the histopathology described as lymphoplasmacytic sclerosing pancreatitis (also known as LPSP or AIP type 1) or idiopathic duct-centric pancreatitis (also known as IDCP or AIP type 2); second, it responds to anti-inflammatory treatments; and third, pancreatic insufficiency and fibrosis can revert to normal.<sup>10–14</sup> How obstructive chronic pancreatitis, pancreatic atrophy, and autoimmune pancreatitis differ from typical calcifying pancreatitis was discussed by Majumder and Chari in a previous Seminar on chronic pancreatitis.<sup>15</sup>

### Epidemiology, demographics and aetiology of chronic pancreatitis

Reliable data on population-wide disease burden of chronic pancreatitis are rare. The prevalence between 2001 and 2013 of adult US Americans with health insurance (48·67 million) was 25·4–98·7 per 100 000 people, depending on search criteria, with a small increase in the male to female ratio of 1·05 (75·2 men vs 71·8 women per 100 000 people), peaking in patients aged 46–55 years.<sup>16</sup> The incidence is estimated to be four to five new cases per 100 000 per year, thus confirming data from a smaller but

comprehensive population-based study from Minnesota.<sup>17</sup> Data from an Italian survey among primary care physicians from one region, a survey of eight pancreas units in Spain, 22 hospitals in China, and a nationwide survey from Japan confirmed similar numbers, with prevalence between 13·5 and 52·4 cases per 100 000, and an incidence of five new cases per 100 000 inhabitants per year.<sup>18–21</sup> A US registry-based analysis published in 2019 found that pancreatitis (acute and chronic) was among the three most common benign gastrointestinal diagnoses and accounted for a 12% increase in emergency room visits since 2006.<sup>22</sup> Common reasons for hospital admission were diabetes complications, pain, and episodes of acute pancreatitis.<sup>23</sup> Whether this rise truly reflects a higher disease burden, or only a greater sensitivity of diagnostic testing, remains unclear. Considering the stable or decreasing tobacco and alcohol use in most western countries, and the probable unchanging prevalence of genetic risk factors, we suspect greater sensitivity of diagnostic testing to be the cause. Approximately 3–35% of patients with a first episode of acute pancreatitis will progress to chronic pancreatitis over 3–8 years.<sup>24,25</sup> Conversely, only about 50% of patients with chronic pancreatitis had previously documented episodes of acute pancreatitis.<sup>26</sup>

Data on the cause of chronic pancreatitis have to be interpreted with caution, because they heavily depend on local standards and are prone to reporting bias. The current paradigm allows for attributing alcohol as the cause when individuals consume more than 80 g of alcohol on average per day for 6–12 years, when a patient has been diagnosed with alcohol addiction in the context

of chronic pancreatitis, or when symptom onset is directly associated with alcohol consumption.<sup>27–29</sup> Whether toxic doses are much lower in some ethnic groups is currently under debate.<sup>30</sup> The term hereditary pancreatitis should be used only if a high-penetrance gene mutation with a dominant trait is detected (almost exclusively in the *PRSS1* gene).<sup>31</sup> In many other cases, no definitive cause can be identified and these cases should correctly be called idiopathic. Of note, in many patients with idiopathic pancreatitis, genetic susceptibility factors and disease modifying mutations are present in conjunction with other environmental or behavioural risk factors.

The North American Pancreatitis Study 2 and North American Pancreatitis Continuation and Validation Study 2 give insight into the demographics of chronic pancreatitis (540 and 521 patients prospectively recruited); in contrast to the common belief that chronic pancreatitis mostly affects middle-aged men with drinking problems, the investigated cohort established that a chronic pancreatitis cohort is much more diverse than this.<sup>32</sup> Of concern, non-white patients had a higher proportion of alcoholic versus other causes (68% non-white vs 42% white; odds ratio [OR] 3·3, 95% CI 1·9–6·0) and a lower percentage of physician-defined genetic susceptibility (11% white vs 1% non-white; OR 8·3, 95% CI 1·2–164·7). This finding might point to social inequity and should prompt further studies into genetic risk factors for chronic pancreatitis in non-white populations. Most of the currently reported mutations were identified in cohorts of white people.<sup>33</sup>

### Risk factors for developing chronic pancreatitis and how they lead to pathophysiological concepts

Table 2 summarises selected causal factors of chronic pancreatitis, their prevalence, and attributed relative risks.

#### Protease dependent mechanism

The initial event leading to pancreatitis is premature intra-pancreatic activation of pancreatic proteases. Mutations in the human cationic trypsinogen (*PRSS1*) cause hereditary pancreatitis with incomplete penetrance and act as a risk factor for sporadic chronic pancreatitis.<sup>34</sup> Hereditary pancreatitis follows an autosomal dominant inheritance pattern, and 90% of affected families carry *PRSS1* p.R122H, p.R122C, or p.N29I loci mutations. These and other rarer mutations lead to a higher likelihood of trypsinogen autoactivation and less effective degradation; both effects are partly dependent on chymotrypsin C (*CTRC*) binding and activity.

A number of potentially trypsin-related mutations that modify risk have been identified. The quite common *CTRC* p.G60= variant is found in 30% of patients with chronic pancreatitis, and increases the risk of chronic pancreatitis by 2·5 to 10 times.<sup>37,41</sup> Conversely, mutations in the anionic trypsinogen (*PRSS2*) were found to decrease the risk of chronic pancreatitis, especially in patients with

#### Panel: Criteria for diagnosing chronic pancreatitis using endoscopic ultrasound

##### The Rosemont classification<sup>7</sup> for endoscopic ultrasound-based criteria for the diagnosis of chronic pancreatitis

Major A criteria:

- Hyperechoic features with shadowing
- Main pancreatic duct calcifications

Major B criteria:

- Lobularity with honeycombing

Minor criteria:

- Lobularity without honeycombing
- Hyperechoic features without shadowing
- Pseudocysts
- Stranding
- Irregular main pancreatic duct
- $\geq 3$  dilated duct branches
- Main pancreatic duct dilatation
- Hyperechoic main pancreatic duct wall

##### Definitive chronic pancreatitis

Consensus endoscopic ultrasound-based criteria consistent with chronic pancreatitis:

- One Major A and three or more minor criteria
- One Major A and major B criteria
- Two Major A criteria

##### Probable chronic pancreatitis

Consensus endoscopic ultrasound-based criteria suggestive of chronic pancreatitis:

- One Major A and three or more minor criteria
- One Major B and three or more minor criteria
- Five or more minor criteria

##### Early or suggestive chronic pancreatitis

More than two of the following seven criteria of endoscopic ultrasound findings, including at least one of criteria (1) to (4):

- 1 Lobularity with honeycombing
- 2 Lobularity without honeycombing
- 3 Hyperechoic foci without shadowing
- 4 Stranding
- 5 Cysts
- 6 Dilated side branches
- 7 Hyperechoic main pancreatic duct margin

Japanese clinical guidelines 2015 adopted from Ito and colleagues (2016)<sup>3</sup> and Rosemont classification criteria adopted from Whitcomb and colleagues (2015).<sup>8</sup>

a background of alcohol misuse.<sup>36,42</sup> A large inversion in the *CTRB1-CTRB2* locus (chymotrypsin B1/B2) found in European populations has a moderate protective effect from alcohol-related chronic pancreatitis by increasing trypsin degradation. In China, the protective variant is found in almost every individual, and therefore plays no role as a disease modifier. A natural counterpart of trypsinogen is the pancreatic secretory trypsin inhibitor (PSTI, the product of the *SPINK1* gene). The most common *SPINK1* mutation p.N34S increases the risk of

	Prevalence among patients with chronic pancreatitis	Risk for developing chronic pancreatitis vs control group	Combinations of risk factor
Excessive alcohol consumption	40–70%	OR 1.7 after initial attack of pancreatitis vs non-drinkers	..
Regular tobacco use	Approximately 60%	OR 2.8 after initial attack of pancreatitis vs non-smokers	Plus excessive alcohol consumption, OR 5.6 after initial attack of pancreatitis vs non-drinkers and non-smokers
<i>PRSS1</i> mutations (hereditary pancreatitis)	3–10%	Autosomal dominant trait with 90% estimated penetrance for the most common variants p.R122H and p.N29I	..
<i>SPINK1</i> mutations	10%	OR 11.0 for the most common p.N34S mutation	..
<i>CTRC</i> mutations	30%	OR 1.4–4.0 (heterozygous vs homozygous for the p.G60= variant)	Plus <i>CFTR</i> or <i>SPINK1</i> mutation, OR 2.0–4.3; plus alcohol, OR 1.7–8.4; plus tobacco, OR 5.4
<i>CTRB1-CTRB2</i> locus mutations	Genome-wide analysis minor allele frequency 0.28	OR 1.4–1.6	Plus one or more mutations in <i>SPINK1</i> , <i>CTRC</i> , <i>PRSS1-PRSS2</i> , or <i>CLDN2-MORC4</i> locus, OR 1.6–24.4
<i>CFTR</i> mutations	Up to 7% (low for non-cystic fibrosis-related variant)	OR 1.5–16.0	Plus <i>SPINK1</i> mutation, OR 3.0–21.1
<i>CPA1</i> mutations	3%	OR 25–80; higher in children <10 years	..
<i>CLDN2</i> or <i>MORC4</i> mutations	Genome-wide analysis minor allele frequency 0.31–0.37	..	Plus alcohol, OR 1.6–2.6
CEL-HYB allele	5%	OR 5.2	Plus alcohol, OR reduced to 2.3
IgG4-related disease (autoimmune pancreatitis type 1)	1–2%	Unknown	..
Pancreatic duct obstruction	2–9%	Unknown	..
Hypertriglyceridaemia	3–13%	Unknown	..
Chronic kidney disease	2–5%	OR 4–5	..

For a full review of risk factors for chronic pancreatitis, see Mayerle and colleagues (2019)<sup>34</sup> and Whitcomb (2019).<sup>35</sup> OR=odds ratio.

**Table 2: Summary of selected aetiological risk factors with estimated OR for developing chronic pancreatitis<sup>39,32,34–40</sup>**

developing chronic pancreatitis by ten times. However, the pathophysiological mechanism is not yet understood, as the inhibitory capacity of mutated *SPINK1* is unchanged. Taken together, these associations strongly suggest a role of trypsin and other proteases in the pathogenesis of chronic pancreatitis. Another, almost forgotten, protease has regained attention. Whole exome sequencing on members of a family with a history of pancreatitis, diabetes, and pancreatic cancer that had been reported some 50 years ago found a missense mutation in the pancreas-specific protease elastase 3b (*CELA3B*).<sup>41</sup> In cell and mouse models, it was confirmed that this variant leads to increased expression and uncontrolled proteolysis.<sup>43</sup>

#### Endoplasmic reticulum stress-related mechanisms

Several rare mutations found in sporadic chronic pancreatitis and in some families cause protein misfolding, secretory blockage, retention, and ultimately result in endoplasmic reticulum stress. Gene variants leading to protein misfolding and endoplasmic reticulum stress in chronic pancreatitis have been found in *PRSS1*, *CPA1* (carboxypeptidase A1), and *CEL* (carboxyl-ester-lipase); *CEL* is also thought to cause exocrine pancreatic insufficiency in patients with maturity-onset diabetes of the

young type 8.<sup>34,44</sup> Blood type B and fucosyltransferase 2 (*FUT2*) non-secretor status are also associated with chronic pancreatitis, with a hypothetical link to protein glycosylation and intracellular protein trafficking.<sup>45</sup>

#### Ductal dysfunction-related mechanism

An association between heterozygous variants of the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene and chronic pancreatitis (in the absence of cystic fibrosis) was first described in the late 1990s. Prevalence of the mutation among patients with chronic pancreatitis is about 2 to 3 times that of the general population. Further risk-modifying variants have been identified, each coming with only small to moderate increase in individual risk.<sup>41</sup> *CFTR* is a master regulator of bicarbonate secretion into the pancreatic duct. Dysregulation of *CFTR* function leads to experimental pancreatitis in rodents. Both alcohol and tobacco smoke lead to *CFTR* dysfunction in mice and humans, which explains an increased prevalence of mutations in patients with alcohol or smoking-related chronic pancreatitis.<sup>46,47</sup>

#### Environmental and behavioural factors

As described earlier, most chronic pancreatitis cases from regions with reliable epidemiological data are associated

with excess alcohol consumption. Tobacco smoking is also prevalent among patients diagnosed with chronic pancreatitis and promotes progression from acute to recurrent acute or chronic pancreatitis. The individual effects are potentiated in patients who drink and smoke (absolute risk approximately 18% for those who drink or smoke vs 30% for those who drink and smoke).<sup>25</sup> In patients who develop chronic pancreatitis from an initial acute attack, the pooled prevalence of alcohol as a risk factor (regardless of smoking status) is 65% (95% CI 48–80%) versus 61% (47–73%) with tobacco.<sup>24</sup> Smoking or alcohol cessation, or both, substantially reduces the risk of disease progression.<sup>48,49</sup>

Alcohol mediates its toxic effects on pancreatic acinar cells via its oxidative and non-oxidative metabolites.<sup>50,51</sup> In addition, ethanol induces microcirculatory disturbances and pancreatic ischaemia, which mediate pancreatic acinar cell injury, activation of the inflammatory cascade, and a necro-inflammatory response, resulting in fibrosis and chronic disease.<sup>52</sup> In the last decade, macrophages and pancreatic stellate cells (an organ-specific, very highly plastic type of myofibroblast) have been at the centre of interest.<sup>53</sup> Animal studies show that alternatively activated macrophages counterbalance pro-inflammatory immune signalling of neutrophils early in the course of disease and promote healing processes,<sup>54</sup> including activation of pancreatic stellate cells.<sup>55</sup> Under prolonged pathological stimuli, however, this response becomes unbalanced, leading to excess deposition of extra cellular matrix and active tissue remodelling and resulting in fibrosis and replacement of functional tissue. Experiments have shown that ethanol and smoke contents damage pancreatic acinar cells directly and activate pancreatic stellate cells.<sup>56–58</sup>

### Establishing a diagnosis of chronic pancreatitis

Making a diagnosis of chronic pancreatitis remains a clinical challenge in many cases. Most diagnostic criteria have been developed using cases of advanced stage classic chronic pancreatitis, with pancreatic calcifications, overt ductal changes, and steatorrhea. The current understanding of a step-wise development, and the desire to identify patients early during disease development, are not met by criteria currently used in routine clinical practice. However, because the disease may come with social stigma, a high degree of certainty should be reached to avoid a false positive diagnosis. A pragmatic, yet conclusive, diagnostic catalogue was proposed in the 2009 evidence-based clinical practice guidelines for chronic pancreatitis from Japan (revised in 2015) and adopted by many centres around the globe, including our own institutions.<sup>5,33</sup> If these criteria are met, the diagnosis of chronic pancreatitis may be established by imaging alone (table 1 and panel). In suspected cases with only probable imaging features of chronic pancreatitis, patients should meet two of three additional clinical criteria: repeated upper abdominal pain; abnormal

serum or urine pancreatic enzyme concentrations (lipase or amylase activity 2–3 times above the upper limit of normal); and abnormal pancreatic exocrine function (faecal elastase concentration <200 µg/g). A typical histology in the absence of pancreatic cancer can support the diagnosis, but obtaining histologies from biopsy samples remains challenging.<sup>59</sup> Whether the suspected cause or the presence of risk factors should be part of the diagnostic algorithm is a matter of ongoing debate.<sup>4,60</sup> The presence of risk factors (eg, heavy smoking, alcohol consumption, or a family history in conjunction with *PRSS1* mutation) can increase the pretest probability of disease diagnosis. However, as up to 20% of people with chronic pancreatitis remain idiopathic, the absence of such risk factors should not rule out a diagnosis of chronic pancreatitis. The definition of early chronic pancreatitis (see earlier) in patients with some clinical features and suggestive, yet not definitive, imaging findings, has been discussed among various expert groups.<sup>4</sup> The suggested criteria (table 1 and panel) need testing in prospective studies.

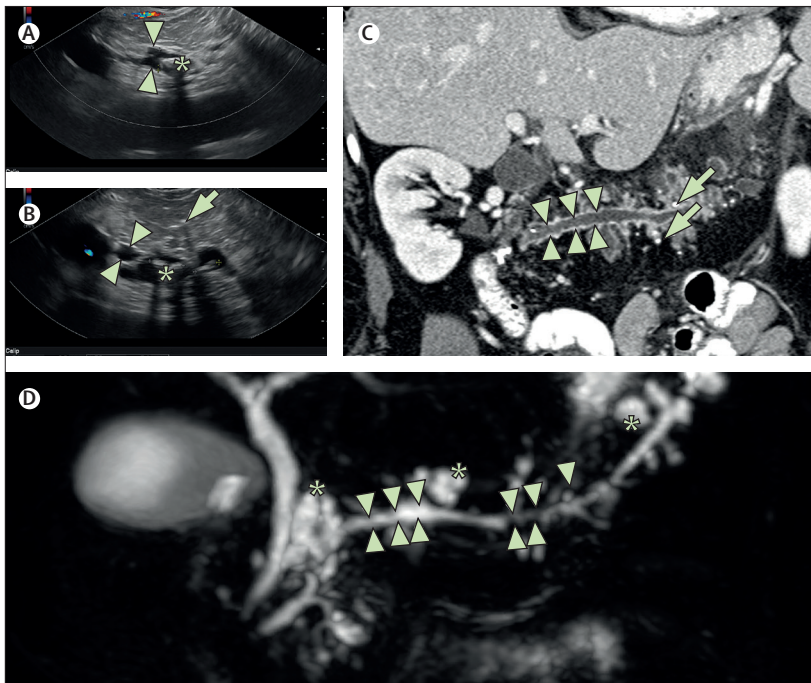
### Diagnostic value of imaging

A 2017 meta-analysis of 43 cohort studies reviewed the diagnostic effectiveness of CT, MRI, endoscopic ultrasound, endoscopic retrograde cholangiopancreatography (ERCP), and transabdominal ultrasound for chronic pancreatitis (table 3, figure 1, figure 2).<sup>61</sup> Results were adopted by the 2016 United European Gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis.<sup>62</sup> Endoscopic ultrasound studies recruited the highest number of patients (n=1249), endoscopic ultrasound and ERCP had the highest sensitivity (81%, 95% CI 70%–89% and 82%, 95% CI 76%–87%), and transabdominal ultrasound had the lowest sensitivity (67%, 95% CI 53%–78%). Specificity was 90% or higher for all techniques, with transabdominal ultrasound reaching 99% (95% CI 89%–100%). However, in head-to-head comparisons using a subset of the data, the specificity of ERCP and endoscopic ultrasound, and the sensitivity of ERCP, endoscopic ultrasound, and CT were significantly higher than for transabdominal ultrasound. There were no significant differences in the sensitivity and specificity between ERCP versus endoscopic ultrasound, magnetic

	Sensitivity (95% CI)	Specificity (95% CI)
CT	75% (66–83%)	91% (81–96%)
MRI	78% (69–85%)	96% (90–98%)
Endoscopic ultrasound	81% (70–89%)	90% (82–95%)
Endoscopic retrograde cholangiopancreatography	82% (76–87%)	94% (87–98%)
Transabdominal ultrasound	67% (53–78%)	98% (89–100%)

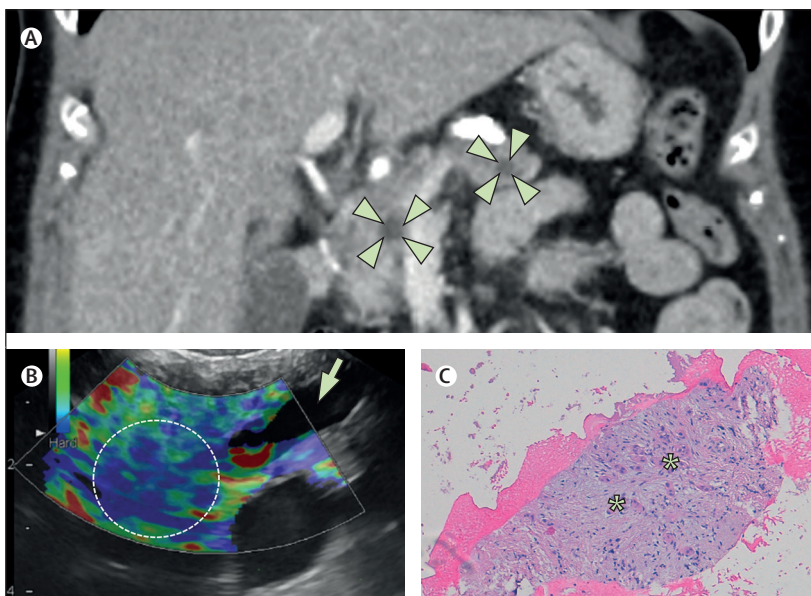
Data modified from Issa and colleagues (2017).<sup>61</sup>

**Table 3: Accuracy of imaging methods for diagnosing chronic pancreatitis**



**Figure 1: Definitive imaging features of chronic pancreatitis**

Imaging of a woman aged in her 60s with a history of chronic pancreatitis and subsequent pancreatic insufficiency for more than 3 decades. Endosonography shows dilated main pancreatic duct (arrowheads; A) with intraductal calcifications (asterisk; A) and hyperechoic features with shadowing (arrow; B) and dilated branch ducts (arrowheads; B). CT imaging shows dilated main duct (arrowheads) and side branches as well as parenchymal calcifications (arrows; C). Magnetic resonance cholangiopancreatography confirms irregular and dilated ducts (arrowheads) as well as small pseudocysts (asterisk; D).



**Figure 2: Imaging features suggestive of chronic pancreatitis in an asymptomatic patient**

A smoker, aged over 60 years, had a long history of type 2 diabetes and imaging features of probable obstructive chronic pancreatitis without symptoms, having marked pancreatic duct dilatation upstream of pancreatic head (arrowheads; A), and dilated side branches on endoscopic ultrasound (arrow; B). An area showed increased stiffness on endoscopic ultrasound elastography in the head of the pancreas (blue area, encircled; B), but no visible tumour. Endoscopic ultrasound-guided fine-needle biopsy uncovered pancreatic ductal adenocarcinoma in fibrotic pancreas (asterisks; C), and the patient underwent a resection with microscopically negative margins. This case illustrates the importance of excluding other differential diagnoses.

resonance cholangiopancreatography (MRCP) versus secretin-enhanced MRCP, or ERCP versus CT endoscopic ultrasound.<sup>61</sup> Guidelines recommend using cross-sectional imaging first, because of its wider availability and non-invasiveness.<sup>6,62</sup> Only when CT or MRI are inconclusive should endoscopic ultrasound be done.<sup>63</sup> ERCP alone should not be used for diagnostic purposes.<sup>1</sup> For better MRCP-based visualisation of pancreatic duct abnormalities (eg, strictures, dilatation of the main duct and its side branches, and irregularities of the ductal wall), the use of intravenous secretin is safe, effective, and increases the sensitivity for early changes.<sup>6,63</sup> Furthermore, it combines high-resolution imaging and detection of exocrine pancreatic insufficiency by semi-quantitative measurement of duodenal filling.<sup>64,65</sup> Standard protocols and reporting guidelines for cross-sectional imaging to ensure quality and comparability have been suggested by the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer in the USA.<sup>66</sup> Novel endoscopic ultrasound-based techniques improve diagnostic yield for specific clinical questions—(eg, contrast-enhanced endoscopic ultrasound may distinguish cystic from solid pancreatic mass lesions in chronic pancreatitis), but need further prospective evaluation.<sup>67</sup> Pancreatic fibrosis is a hallmark of chronic pancreatitis and results in increased tissue stiffness, while studies unanimously report higher values in quantitative elastography of the pancreatitis parenchyma compared with healthy controls.<sup>68</sup> However, so far, diagnostic accuracy of endoscopic ultrasound elastography does not outperform conventional endoscopic ultrasound in chronic pancreatitis, and the method must be considered as complementary (table 3, figure 1, and figure 2).<sup>69,70</sup>

### Evaluating pancreatic exocrine function

A loss of functional acini, ductal epithelial dysfunction, duct obstruction, or inactive pancreatic enzymes, resulting in pancreatic exocrine insufficiency, are found in acute and chronic pancreatitis, and in pancreatic cancer. In the presence of other features of chronic pancreatitis, such insufficiency supports the diagnosis and also helps with staging.<sup>6</sup> Pancreatic exocrine insufficiency should be recognised early during management, because it is associated with malnutrition, endocrine dysfunction, micronutrient depletion, and symptoms such as bloating and diarrhoea, and is a risk for osteoporosis and cardiovascular events.<sup>71–75</sup> Measuring faecal elastase-1 is a cost-effective, non-invasive, and widely available test of pancreatic exocrine function and, although it can be insensitive for detecting mild or moderate pancreatic exocrine insufficiency, the risk of it missing severe dysfunction is low.<sup>6,76</sup> The <sup>13</sup>C mixed triglyceride breath test is a very sensitive alternative test which, unlike faecal elastase-1 measurement, also has the advantage of giving a functional read-out, and can be used to measure the effectiveness of therapy.<sup>77–79</sup> Measuring duodenal filling on secretin-enhanced MRCP gives at least a semi-quantitative

measure of exocrine function and should be assessed when there are additional indications for MRCP.<sup>80</sup>

### Evaluating pancreatic endocrine insufficiency

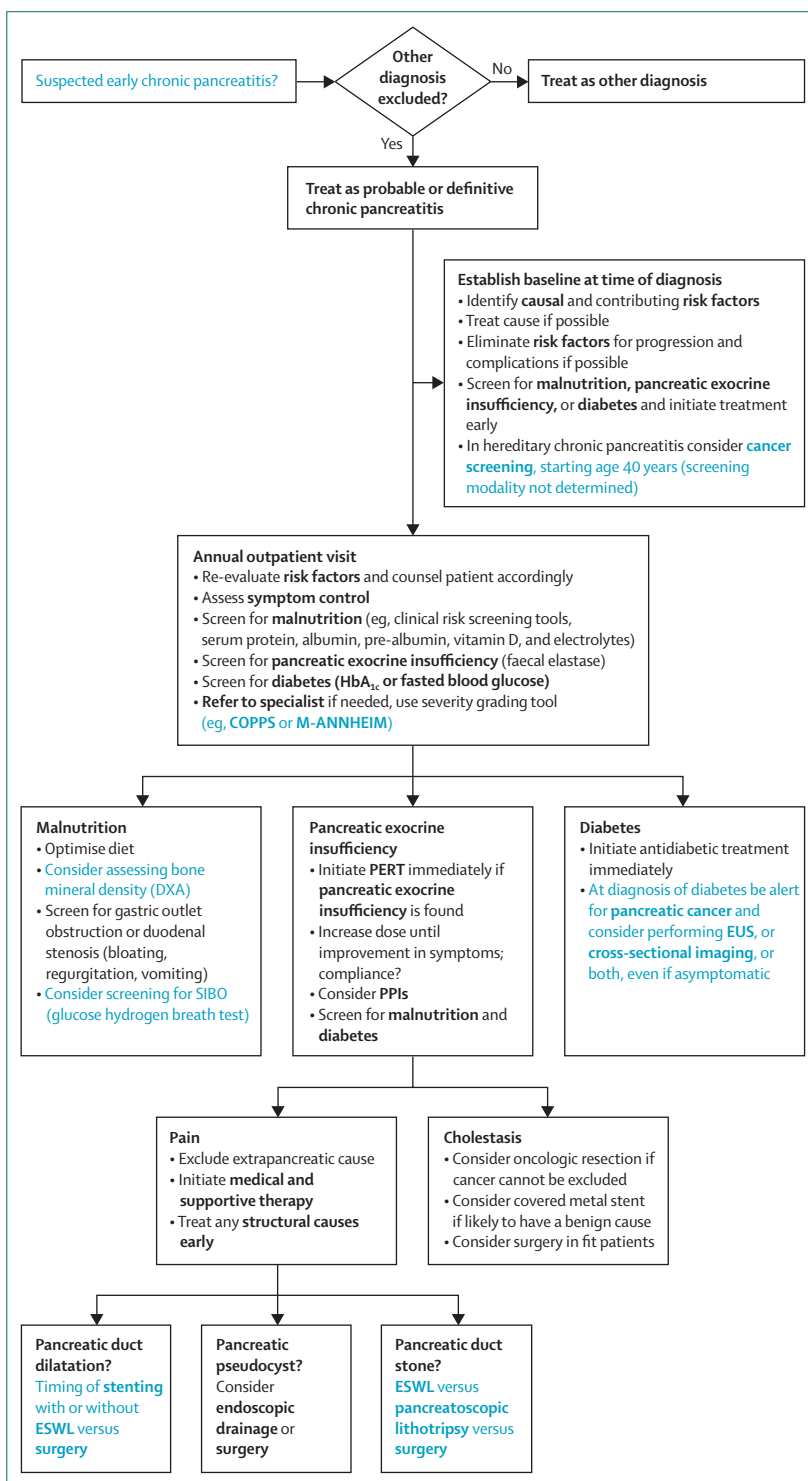
We estimate that the prevalence of diabetes in patients with chronic pancreatitis ranges from 25% to 80%, with onset occurring 10–20 years after the time of diagnosis. Pancreas-specific risk factors for the progression to endocrine insufficiency and diabetes include ongoing heavy alcohol consumption, pancreatic exocrine insufficiency, pancreatic calcifications, and pancreatic tail resection.<sup>81,82</sup> A diagnosis of type 3c diabetes (defined as pancreatic islet dysfunction and islet loss as a result of diseases of the exocrine pancreas) can be made if the following criteria are fulfilled: presence of pancreatic pathology on imaging together with exocrine pancreatic insufficiency and the absence of autoimmune markers suggestive of type 1 diabetes. A decrease in  $\beta$ -cell function, absence of insulin resistance, loss of incretin secretion, and low fat-soluble vitamin concentrations can further support the diagnosis.<sup>83,84</sup> To screen for diabetes, measurement of glycated haemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) or fasting glucose are equally valid.

### Biomarkers for chronic pancreatitis

At this moment no individual biomarker or biomarker panel can be recommended for diagnosing chronic pancreatitis.<sup>62</sup> A potential use for a diagnostic biomarker would be as a rule-in or rule-out tool early in the disease course in patients who are at risk for chronic pancreatitis but do not yet meet classic imaging criteria. Studies have explored the diagnostic value of single proteins and metabolomic and microRNA signatures in blood and urine of patients with chronic pancreatitis, but were too small to be conclusive.<sup>85–88</sup> Low, rather than elevated, plasma activity of amylase showed high specificity (of 0.94 if lower than 17.3 U/L) for diagnosis of chronic pancreatitis in two independent cohorts from Europe.<sup>89</sup> Our own group has identified and validated a plasma metabolome panel, comprised of eight markers in a cohort of 670 patients from four centres, that can successfully discriminate between chronic pancreatitis and controls with an area under the curve of 0.85 (95% CI 0.81–0.89) (Beyer G, unpublished). A metabolomics approach to distinguish between pancreatic cancer and chronic pancreatitis has already been established.<sup>90</sup> Similar diagnostic accuracy was achieved using a cytokine signature identified from chronic pancreatitis and control serum samples in 81 participants using an antibody-based Luminex assay (area under the curve of 0.86, 95% CI 0.77–0.94).<sup>91</sup> Whether biomarkers are shown to have sufficient validity and clinical utility for routine practice remains to be seen.

### Management

A summary of recommendations based on available guidelines and expert consensus is shown in figure 3.



**Figure 3: Treatment algorithm for chronic pancreatitis based on available guidelines and expert consensus<sup>1,6,92,93</sup>**

Bold text indicates that topic is discussed in detail in body of the manuscript. Blue text indicates areas of ongoing investigation. COPPS=Chronic Pancreatitis Prognosis Score. DXA=dual-energy x-ray absorptiometry. ESWL=extracorporeal shock wave lithotripsy. EUS=endoscopic ultrasound. HbA<sub>1c</sub>=glycated haemoglobin A<sub>1c</sub>. M-ANNHEIM=Mannheim classification and prognosis score. PERT=pancreatic enzyme replacement therapy. PPIs=proton pump inhibitors. SIBO=small bowel intestinal overgrowth.

### Scoring severity and disease activity in chronic pancreatitis

Scoring the severity of chronic pancreatitis is a clinical challenge, because no existing clinical score or classification has been developed to predict short-term and medium-term outcomes.<sup>1,6,94</sup> The M-ANNHEIM classification<sup>95</sup> and the Chronic Pancreatitis Prognosis Score<sup>33</sup> are the only clinical classifications that include a severity index. M-ANNHEIM also includes stage, aetiology, and clinical findings and, although its development was based on expert opinion, it identifies patients who profit from surgery or endoscopy.<sup>95-98</sup> The Chronic Pancreatitis Prognosis Score, which was developed by our group and validated in patients from Denmark, follows a different approach: a large panel of clinical and laboratory parameters of chronic pancreatitis was prospectively correlated with increased risk of hospital admission in the following 12 months. It was assumed that hospitalisation was a strong endpoint and a good indicator of disease burden. The five best fitting parameters (body-mass index, HbA<sub>1c</sub>, C-reactive protein, platelet count, and pain intensity) were combined into a simple numeric score, similar to the Child-Pugh Score for cirrhosis.<sup>33</sup> Large-scale international validation is underway. Whether histology correlates to disease activity is unclear (appendix p 1).

See Online for appendix

### Pain management and medical therapy

Pain is the primary symptom in patients with chronic pancreatitis, being reported by 75% of patients at presentation, and by almost 100% over time.<sup>99</sup> It thus has a great effect on QOL and disability.<sup>99</sup> Patients with a cause involving alcohol are most likely to have pain, whereas late-onset chronic pancreatitis is reported to be less painful.<sup>92</sup> Although the pathomechanism of chronic pancreatic pain is poorly understood, pancreatic inflammation, duct obstruction, and central nervous changes have been shown to contribute to the development of symptoms and need to be addressed separately for symptom control.<sup>92</sup> For pain assessment, one-dimensional tools such as the Numerical Pain Rating Scale are widely recommended, but multidimensional scores such as the Brief Pain Inventory or the McGill Pain Questionnaire are preferred.<sup>92</sup> In severe cases, verbal pain assessment can be complemented by quantitative sensory testing (a non-invasive method to test vibration and temperature sensation), which can also be used to evaluate treatment response. Furthermore, quantitative sensory testing could help to unmask irreversible central neuroplastic changes that make interventional treatment of pancreatic pain less likely to be successful.<sup>100</sup> Cessation of alcohol consumption and smoking should be strongly advised and supported in all patients with painful chronic pancreatitis. Pancreatic enzyme replacement therapy and nutritional therapy to prevent malnutrition should be optimised, although do not contribute directly to pain relief.

The choice of analgesic needs to follow local standards, and adherence to the WHO pain relief ladder is recommended.<sup>92</sup> Non-opioid analgesics are the cornerstone of pain treatment; co-analgesics should also be tried and interventional therapy (such as surgery) be considered before starting opioids, given the adverse effects of opioids (eg, constipation, nausea, sedation, increased risk of falls, and risk of dependence and substance misuse). Co-analgesics such as antidepressants and anticonvulsants (eg, gabapentin, pregabalin) have shown effectiveness in treating chronic visceral and neuropathic pain in chronic pancreatitis, and can reduce the need for opioids.<sup>92,101</sup> Alternative analgesics such as esketamine are currently being investigated for this indication.<sup>102</sup>

If opioids are necessary, they should be given in a long-acting oral form. Physicians need to be aware of their side-effects and be competent in their management.

Pharmacological treatments should be embedded in an interdisciplinary approach, and patients with decreased QOL because of pain should be referred for psychological therapy, such as cognitive-behavioural therapies, neuromodulation, or similar possibilities.<sup>92</sup> To determine the best treatment, patients should be evaluated by an interdisciplinary team early in the course of pancreatitis.

### Endoscopic and surgical therapy of pain in chronic pancreatitis

In general, interventional therapy for pain in chronic pancreatitis should be reserved for patients with recurrent attacks of pain that are unresponsive to non-opioid therapy and those with moderate to marked morphological changes, and be done at experienced centres. It is important to stress that morphology and symptoms do not correlate well, and many patients with substantial duct obstruction or calcifications may have only moderate symptoms, and vice versa.<sup>103</sup> Additionally, none of the available interventional trials (endoscopic or surgical) included a sham intervention as a control, so share the limitation of potential selection bias and unknown placebo effect.<sup>104</sup> Whether surgical or endoscopic therapy should be offered first is a matter of an ongoing debate. Although criticised for weaknesses in the study design, two randomised controlled trials showed better long-term pain relief with surgery than endoscopy.<sup>105-107</sup> The explanation for this effect could be that surgical treatment not only decreases ductal hypertension by providing drainage, but also removes inflamed tissue that induces neural alterations and pain.<sup>108,109</sup> Patients with a large inflammatory mass of the pancreatic head, distal pancreatic stenosis, and calcifications of the pancreatic head might be difficult to treat by endoscopy.<sup>1</sup> In contrast, patients with a symptomatic pancreatic duct obstruction in the pancreatic head or neck, together with an upstream duct dilatation, could benefit from endoscopic therapy. In both cases, multiple plastic stents and fully covered self-expandable metal stents are safe and effective options for the relief of pancreatic outflow obstruction.<sup>110,111</sup>

Novel treatment strategies include the use of biodegradable stents (appendix p 3).<sup>112</sup> If endotherapy does not lead to immediate symptom relief, without the need for repetitive endoscopies, a multidisciplinary team discussion should strongly consider surgery.

Surgical outcomes are better if patients are referred within 3–5 years from onset of symptoms and have had fewer than four endoscopic interventions before surgery.<sup>89</sup> The ESCAPE trial<sup>113</sup> (88 patients randomised) compared surgery early (ie, 2–6 months) after starting opioids versus a step-up approach including medical therapy and endoscopy (with and without extracorporeal shock wave lithotripsy). Although results suggested better short-term pain relief with early surgery, the investigated population was highly selected and even in the early surgery group almost half of the patients reported only minimal pain relief.<sup>114</sup>

The type of surgery depends on the anatomy, disease course, and local preferences.<sup>115</sup> Pancreatic head enlargement with pancreatic duct dilatation should be treated with a (partial) pancreatic head resection. This can be done by duodenum-preserving techniques or the Kausch-Whipple procedure.<sup>116</sup> Both techniques are equally effective in terms of pain relief and complications, but partial pancreatic head resections (such as the Frey procedure or the Berne modification) involve a shorter hospital stay and quicker rehabilitation after surgery (appendix p 4).<sup>93,117–119</sup> In cases with duct dilatation without pancreatic head enlargement, drainage procedures or segmental resections might be indicated (appendix p 4).<sup>115</sup> Pancreatic tail resections are rarely indicated, and carry the risk of diabetes.<sup>115</sup> Total pancreatectomy with auto-islet transplantation is still not widely available outside the USA. Indications include painful pancreatitis, especially in younger patients, or the prevention of pancreatic cancer in patients with hereditary pancreatitis. However this procedure needs careful consideration, as long-term results show a mixed response, with decreasing insulin independence after 5 years (38–27%).<sup>81,104,121,122</sup>

### Treatment of pancreatic duct stones

Stones obstructing the pancreatic duct should be treated if they cause symptoms.<sup>1</sup> The method of treatment should be assessed by an interdisciplinary team, considering local complications and the anatomy of the patient.<sup>1,106</sup> Endoscopic stone extraction, with or without protective stenting, is still the treatment of choice, especially if stones are located in the head or neck of the pancreas, and if there are no more than three stones. In contrast, surgical treatment is preferred for more distal stones, and when local complications prevail.<sup>1,106,107</sup> In patients with stones that measure 2–5 mm and are visible on x-ray, additional extracorporeal shock wave lithotripsy can be offered. This clears stones in 54–100% of cases, with opioid dose reduction in 80% of cases, and is also an attractive alternative for patients who are unwilling or

unfit for surgery.<sup>123</sup> The use of pancreatoscopy-directed electrohydraulic or laser lithotripsy for obstructing pancreatic stones is an emerging technique.<sup>124,125</sup> Preliminary studies suggest favourable results, with the advantage of less resource-intensive equipment compared with extracorporeal shock wave lithotripsy. However, this technique obviously requires access to the pancreatic duct (appendix pp 3–4).

### Management of biliary stenosis

Until a few years ago, and in contrast to pancreatic duct stenosis, biliary stenosis due to chronic pancreatitis was a complication referred directly for surgery.<sup>1</sup> Nowadays, this is still true in patients with severe pain, suspicion of pancreatic cancer, or additional local complications. A meta-analysis of 22 cohort studies, 1298 patients in whom benign common bile duct stenosis (including chronic pancreatitis) was treated with covered self-expandable metal stents, showed excellent long-term results, with resolution of stenosis in 83% of patients (95% CI 78–87%).<sup>126</sup> Moreover, insertion of multiple plastic stents is as effective as covered self-expandable metal stents, but requires additional stents and is more time-consuming.<sup>127</sup>

### Management of pancreatic fluid collections and pseudocysts

Pancreatic fluid collections and pseudocysts (defined as mostly liquid-containing collections with high lipase activity) require treatment only if symptomatic or larger than 4 cm and persistent for more than 3–6 months.<sup>6</sup> Endoscopic ultrasound-guided transmural drainage into the stomach or duodenum is the preferred treatment, and double-pigtail plastic stents are usually sufficient to achieve clinical success,<sup>128,129</sup> but covered lumen-apposing metal stents have emerged as an alternative and are now widely used.<sup>130</sup> Plastic stents should be left in place for a minimum of 3 months to prevent recurrence.<sup>131</sup> Metal stents need to be removed or replaced earlier to prevent migration and bleeding (appendix p 2).<sup>132,133</sup> Although pseudocysts can be treated safely and effectively by endoscopy in most cases, surgical internal drainage of cysts can be done in cases of endoscopic failure.<sup>1</sup>

In cases of known pancreatic duct disruption detected during follow-up or in recurrent pancreatitis, additional transpapillary stenting of the pancreatic duct is recommended; otherwise there appears to be no added benefit for dual stenting.<sup>134</sup> If endoscopic treatment is not successful, surgical drainage or pancreatic left resection can usually be safely performed, in these complex and rare cases.<sup>1</sup> Contraindications for endoscopic drainage include vascular complications such as pseudo-aneurysm of the splenic artery or haemorrhagic pseudocysts.<sup>6,2</sup> For these cases, endovascular therapy before endotherapy, or primary surgery need to be considered.

### Pancreatic enzyme replacement therapy, nutritional therapy, and nutritional markers

Chronic pancreatitis increases the risk of malnutrition caused by exocrine insufficiency and postprandial abdominal pain. A long-term follow-up study in Spain showed that pancreatic exocrine insufficiency is associated with excess mortality (hazard ratio 2.59, 95% CI 1.42–4.71)<sup>135</sup> and a meta-analysis indicated that pancreatic enzyme replacement therapy effectively relieves symptoms and improves nutritional status.<sup>136</sup> A large randomised controlled trial in unselected non-critically ill inpatients showed that nutritional evaluation and treatment can lower morbidity and mortality.<sup>137</sup> All patients with chronic pancreatitis and pancreatic exocrine insufficiency, or signs of malnutrition should be treated with 40 000–50 000 lipase units of pancreatic enzymes per meal, and dose should be increased until relief of symptoms occurs. In non-responders, an indirect pancreatic function test (eg, <sup>13</sup>C-mixed triglyceride breath test with pancreatic enzyme replacement therapy) can be obtained. If needed, proton pump inhibitors increase the efficacy of treatment.

All patients with chronic pancreatitis should undergo regular nutritional assessment and counselling to screen for malnutrition.<sup>62</sup> This process includes clinical tools such as the Nutritional Risk Screening 2002 and measurement of nutritional markers, (eg, protein, albumin, pre-albumin, vitamin D, and electrolytes).<sup>138</sup> No pancreatitis-specific diet has been shown to be more effective than a healthy diet. Gastroenterologists or primary care physicians should be aware of an increased risk of osteoporosis.<sup>74</sup>

### Treatment of endocrine insufficiency

The management of type 3c diabetes follows general recommendations for diabetics. Medical treatment should be accompanied by a healthy lifestyle with regular exercise and a balanced diet. Optimising pancreatic enzyme replacement therapy increases duodenal sensing and uptake of complex nutrients, and therefore stabilises blood sugar concentrations. Patients with type 3c diabetes are at an increased risk for hypoglycaemia due to a lack of counter regulation and should be counselled accordingly. Insulin is often the treatment of choice, but in mild hyperglycaemia (HbA<sub>1c</sub> <8%) metformin has also been recommended. Sulfonylureas should be avoided. Although glinides, thiazolidinediones, α-glycosidase inhibitors, incretin-based therapies, and SGLT2 inhibitors have not been tested in randomised trials, they might be beneficial in some circumstances.<sup>62</sup> In addition to its glucose-lowering effect, a meta-analysis of 12 observational studies showed that metformin reduced the risk of pancreatic cancer development in people with diabetes (standardised rate ratio 0.73, 95% CI 0.56–0.96).<sup>139</sup>

### Pancreatic cancer risk and surveillance

The connection between chronic pancreatitis and pancreatic cancer is complex because common risk factors

and the disease course influence the rate of malignant transformation. Pancreatic cancer is estimated to become the second to third most common cause of cancer-related deaths by 2030, because of late diagnosis and poor therapeutic options.<sup>140</sup> The risk of developing pancreatic cancer in patients with chronic pancreatitis is markedly increased, with a relative risk between 6.09 (95% CI 3.79–9.79) and 11.77 (95% CI 6.88–20.12) in a meta-analysis,<sup>141</sup> but is potentially confounded by smoking, which poses an independent risk factor.<sup>142</sup> The risk for pancreatic cancer strongly increases in patients with hereditary pancreatitis, and could be as high as 70 times that of a control population.<sup>8,143</sup> Regardless of gene-carrier status, patients with hereditary chronic pancreatitis should be included in a screening programme from age 40 years, or from 20 years after the diagnosis of chronic pancreatitis.<sup>144</sup> Screening includes yearly visits to a specialised centre with HbA<sub>1c</sub> measurement, and alternating MRI and endoscopic ultrasound imaging. Newly diagnosed diabetes can be an early indicator of pancreatic cancer and should lead to further tests in all patients with chronic pancreatitis.

### Conclusion and future directions

The past 10 years have shed light on risk factors, susceptibility genes, and the pathophysiology of pancreatitis. Novel imaging techniques, such as secretin-enhanced MRI, contrast-enhanced endosonography, and elastography-supported endosonography have advanced the diagnostic options and their sensitivity for chronic pancreatitis. Interventional endoscopy and surgery allow for effective, long-lasting symptomatic treatment in selected patients. Nevertheless, even in 2020 we do not have evidence that morphology follows function, and have no surrogate markers for severity staging and disease monitoring. Without the possibility of accurate staging and disease monitoring, trials that investigate the effectiveness of causative treatments will remain largely fruitless. Immune-modulating therapies for treating sterile inflammation have been approved, and computer modelling in chronic pancreatitis suggests that similar therapeutics might be effective for chronic pancreatitis.<sup>145</sup> In conclusion, chronic pancreatitis is increasing in prevalence, the resulting medical need and socioeconomic impact are high, and clinical trials are urgently needed to advance patient care.

### Contributors

All authors drafted the article outline and prepared the manuscript. GB and JW did the literature research and assessment. GB, JW, and JM prepared the figures. GB, MML, and JM prepared the tables. AH, JW, MML, and JM critically reviewed the article. GB and JM submitted the manuscript.

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