

## CLINICAL PRACTICE GUIDELINE

# Chronic Pancreatitis—Definition, Etiology, Investigation and Treatment

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## SUMMARY

**Background:** Chronic pancreatitis has an annual incidence of 23 per 100 000 population in Germany, where it accounts for about 10 000 hospital admissions per year. The disease shortens the life expectancy of its sufferers by an average of 23%. It most commonly affects men aged 20 to 40.

**Methods:** A systematic search for pertinent literature retrieved 19 569 publications, 485 of which were considered in the creation of this guideline, including 67 randomized controlled trials (RCTs). A consensus conference reached agreement on a total of 156 definitions and recommendations.

**Results:** The identification of genetic risk factors for pancreatitis is now well established. The diagnosis is made mainly with ultrasonography of the pancreas; if the findings are uncertain, further studies can be performed, including endosonography and endosonographically assisted fine-needle puncture for the examination of small foci of disease. Computed tomography and MRI/magnetic resonance cholangiopancreatography are supplementary diagnostic methods. Endoscopic retrograde cholangiopancreatography is now used almost exclusively for treatment, rather than for diagnosis. 30% to 60% of patients develop complications of chronic pancreatitis, including pseudocysts, bile-duct stenosis, or medically intractable pain, which can be treated with an endoscopic or surgical intervention. Patients with steatorrhea, a pathological pancreatic function test, or clinical evidence of malabsorption should be given pancreatic supplementation. The head of the pancreas should be resected if it contains an inflammatory pseudotumor.

**Conclusion:** The management of patients with chronic pancreatitis requires close interdisciplinary collaboration, as it can be treated medically and endoscopically as well as surgically.

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Most patients with chronic pancreatitis are treated on an outpatient basis, yet a large number are still hospitalized: There were 10 267 inpatient admissions for chronic pancreatitis (ICD-10 code K86) in Germany in 2008, according to the German Federal Statistical Office. The incidence of the disease is rising and has now reached 23 cases per 100 000 persons per year in Germany (1). One-third of patients can no longer work in their original profession, and 40% become temporarily or permanently disabled because of the disease (2). The mortality of persons with chronic pancreatitis exceeds that of the general population by a factor of 3.6 (3). Reported mortality figures over time periods of 6 to 10 years range from 13% to 20% (4). The 10-year survival rate is 70% and the 20-year survival rate is 45%, compared to 93% and 65% in age-matched controls (4).

The goal of this German, Austrian, and Swiss guideline is to summarize and evaluate current knowledge of the definition, etiology, diagnostic investigation, and treatment of chronic pancreatitis in adults and children and to derive evidence-based clinical recommendations.

## Methods

After a systematic search of the literature, experts from 10 German, Swiss, and Austrian medical societies (*e-Boxes 1 and 2*) analyzed 19 569 publications (1400 as whole text, including 67 randomized controlled trials [RCTs], *eTable 1*) and evaluated them according to the Oxford criteria for evidence-based medicine (*eTable 2*). After an internal consensus had been reached in each of 10 working groups (*eBox 1*), a joint consensus conference agreed on the 156 definitions and recommendations that were issued in this S3 guideline.

A total of 485 pertinent publications were considered in the final evaluation and are cited in the complete version of the guideline, which has been published elsewhere with a detailed description of the method by which it was produced (5). The guideline can be downloaded at [http://www.awmf.org/uploads/tx\\_szleitlinien/021-0031\\_S3\\_Chronische\\_Pankreatitis\\_08-2012.pdf](http://www.awmf.org/uploads/tx_szleitlinien/021-0031_S3_Chronische_Pankreatitis_08-2012.pdf) and at [www.dgvs.de/index\\_2444.php](http://www.dgvs.de/index_2444.php). It will be valid for the next five years.

**TABLE 1**

**The sensitivity and specificity of pancreatic function tests<sup>1</sup> (37)**

Test	Mild exocrine insufficiency Sensitivity (%)	Moderate exocrine insufficiency Sensitivity (%)	Severe exocrine insufficiency Sensitivity (%)	Specificity (%)	Level of evidence
F-elastase-1(stool elastase)	54%	75%	95%	85% (96%/79%) <sup>2</sup>	1a/b
Qualitative stool fat determination	0%	0%	78% <sup>3</sup>	70% <sup>3</sup>	
Chymotrypsin activity in stool	<50%	ca. 60%	80–90%	80–90%	1a/b
<sup>13</sup> C breath tests (mixed triglycerides)	62–100%		90–100%	80–90%	1b/2b

<sup>1</sup> The direct, invasive pancreatic function tests (secretin test and secretin/pancreozymin test) are used as reference tests; therefore, no sensitivity or specificity figures are given for them.

<sup>2</sup> Mean specificity. In parentheses: specificity with different controls (healthy probands, patients).

<sup>3</sup> Figures for quantitative stool fat determination

**Definition**

Chronic pancreatitis is a disease of the pancreas in which recurrent episodes of inflammation lead to replacement of the pancreatic parenchyma with fibrotic connective tissue (6). Consequently, the exocrine and endocrine functions of the pancreas are progressively lost. Further characteristic complications include:

- pseudocysts
- stenosis of the pancreatic duct
- duodenal stenosis
- vascular complications
- compression of the bile ducts
- malnutrition
- chronic pain.

Pain is the main symptom of patients with chronic pancreatitis. The disease raises the risk of developing pancreatic carcinoma by a factor of 16 and, in patients who also smoke, by a factor of 25 (7). Among patients with chronic pancreatitis, the lifetime risk of pancreatic carcinoma is 5% at most.

The relative risk of pancreatic carcinoma in patients with chronic pancreatitis is 13.1% (95% confidence interval [95% CI] 6.1%–28.9%); in patients with hereditary pancreatitis, it is 69% (95% CI 56.4%–84.4%) (8).

**The causes of chronic pancreatitis**

Alcohol has been identified as a definitive cause of chronic pancreatitis. Persons who drink 80 g or more of alcohol per day over a period of 6–12 years are at risk of developing chronic pancreatitis (9).

Patients with chronic pancreatitis who smoke should be urgently advised to enroll in a smoking-cessation program (level of evidence: 3b, recommendation grade: A, strong consensus). Large-scale cohort studies, some of them prospective, including as many as 695 patients have shown that smoking accelerates the progression of chronic pancreatitis (10).

**Hereditary factors in chronic pancreatitis**

Mutations of the cationic trypsinogen gene (*PRSS1*) lead with 80%–93% penetrance to autosomal dominant chronic pancreatitis (level of evidence: 1c, recommendation grade: A, strong consensus) (11, 12).

The prevalence of hereditary pancreatitis is 1/300 000 (7). 66%–68% of all patients with hereditary pancreatitis have a mutation in the *PRSS1* gene (11, 12). Other genetic risk factors that are much more common in patients with sporadic pancreatitis are variants in the *SPINK1* gene (7) and the *CFTR* gene (13).

**Genetic testing for suspected hereditary pancreatitis**

The *PRSS1* gene should be analyzed for mutations in patients with a positive family history (one or two first-degree relatives with idiopathic pancreatitis), those with two or more episodes of acute pancreatitis of no identifiable cause before age 25, or those with idiopathic chronic pancreatitis with onset before age 25 (level of evidence: 3b, recommendation grade: B, consensus).

Testing for mutations in the *SPINK1*, *CFTR*, and *CTRC* genes and other associated genetic changes can be performed in a research setting or for further etiological investigation (level of evidence: 3b, recommendation grade C, consensus).

**The development and clinical manifestations of exocrine pancreatic insufficiency**

The characteristic manifestations of exocrine pancreatic insufficiency are abdominal discomfort, steatorrhea, and signs of malnutrition. Exocrine pancreatic insufficiency may arise even before chronic pancreatitis is diagnosed but becomes more common starting about 10 years after the onset of overt manifestations of chronic pancreatitis. Decompensation, with steatorrhea, occurs only when lipase secretion

is reduced by more than 90% to 95% (14). Exocrine pancreatic insufficiency can cause malnutrition and weight loss even in the absence of symptomatic steatorrhea (15). Subclinical, mild, or moderate exocrine insufficiency markedly elevates the risk of osteoporosis, fractures, and vitamin deficiencies, particularly of vitamins D and E. The absence of morphological evidence of chronic pancreatitis is no guarantee of normal pancreatic function.

The clinical evaluation should include a noninvasive test of pancreatic function, e.g., a fecal elastase test (with specific antibodies). Alternatively, a breath test with <sup>13</sup>C-marked lipids can be used (Table 1) (level of evidence: 5, recommendation grade: B, consensus, clinical consensus in favor of noninvasive testing).

### Imaging studies in chronic pancreatitis

The diagnosis of chronic pancreatitis is based on clinical, morphological, and functional evidence. These three lines of evidence are not closely correlated with one another and therefore play complementary roles in the diagnosis of the disease.

After history-taking and physical examination, the initial imaging study is ultrasonography of the pancreas. If chronic pancreatitis is clinically suspected, but ultrasonography reveals less than definitive evidence (an inhomogeneous organ with a pancreatic duct of normal width), endosonography (EUS) should follow (16). Tissue can be obtained by endosonographically assisted fine-needle puncture (EUS-FNP) for the cytological or histological differentiation of foci of disease (and the ascertainment of autoimmune pancreatitis, if present). Computed tomography (CT) and MRI with magnetic resonance cholangiopancreatography (MRCP) are complementary diagnostic methods for the further evaluation of unclear pancreatic changes. In particular, MRCP should be performed to obtain detailed information about the pancreatic duct system (level of evidence: 2a, recommendation grade: B, consensus) (Table 2).

No prospective randomized studies have yet been performed to compare ultrasonography (US), EUS, and CT for the diagnostic evaluation of chronic pancreatitis. Prospective studies have only compared endoscopic retrograde cholangiopancreatography (ERCP) with EUS, MRCP with EUS, and US with ERCP. Endosonography is the most sensitive diagnostic test for chronic pancreatitis. Comparative studies have shown that EUS is superior to MRCP for the diagnosis of early forms of the disease. ERCP is associated with higher morbidity (5%–10% overall; 3.47% post-ERCP pancreatitis) and mortality (0.3%) and therefore should no longer be performed as a solely diagnostic procedure (17).

Endoscopic retrograde pancreatography (ERP) is still indicated in rare cases, e.g., when both EUS and MRI/MRCP have been performed without yielding a definitive diagnosis. Diagnostic ERP can also be useful in suspected cases of autoimmune pancreatitis (18)

TABLE 2

The sensitivity and specificity of imaging studies for the diagnosis of chronic pancreatitis (5)

Type of study	Sensitivity	Specificity	Level of evidence
CT	n/a	n/a	2b
ERCP	70–80%	80–100%	2a
MRCP	88%	98%	2b
US	60–81%	70–97%	2a
EUS	80–100%	80–100%	2a

CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; MRCP, magnetic resonance cholangiopancreatography; US, ultrasonography; EUS, endoscopic ultrasonography, n/a, not available

(level of evidence: 4, recommendation grade: C, strong consensus).

The different criteria for the various imaging modalities in use should be modified and applied in accordance with the Cambridge classification (Table 3) (level of evidence: 2a, recommendation grade: B, strong consensus).

### Indications for interventional or surgical treatment

30%–60% of patients with chronic pancreatitis develop complications of their disease requiring either interventional or surgical treatment. These include

- strictures of the common bile duct,
- inflammatory masses,
- pancreatic pseudocysts, and
- pancreatic duct stones.

In the following paragraphs, we discuss the indications for treatment. Persons who persistently need to take analgesic medication for pain should receive either interventional or surgical treatment (level of evidence: 2b, recommendation grade: B, consensus).

Pain relief can be achieved by endoscopic techniques in 66% of cases (19). Surgery is more likely to bring long-term relief compared to endoscopic techniques, but is associated with higher morbidity (30.6%–36% [20, 21]) and mortality for pancreatic resective techniques (6.1–6.4% [22]).

Only two studies have provided level 1b evidence from a direct comparison of surgery with endoscopy (23, 24). Both showed that surgical drainage yielded better results over the long term regarding pain reduction.

Pancreatic duct stones and stenoses that cause pain by blocking the outflow of pancreatic secretions, induce recurrent bouts of disease, maintain a pseudocyst or fistula, or cause other complications can be treated either endoscopically or surgically (level of evidence: 4, recommendation grade: D, strong consensus).

When resectable pancreatic carcinoma is suspected, the treatment should be surgical (level of evidence: 2b, recommendation grade: A, consensus).

**TABLE 3**

**Evaluation criteria for various diagnostic techniques according to the Cambridge classification**

Endoscopic retrograde cholangiopancreatography (ERCP)	
Cambridge 0	No abnormalities with complete visualization of the pancreatic duct
Cambridge 1	Fewer than 3 abnormal side branches, main duct normal
Cambridge 2	More than 3 abnormal side branches, main duct normal
Cambridge 3	More than 3 abnormal side branches, main duct pathological
Cambridge 4	As in 3, with cysts, duct stones, strictures, involvement of neighboring organs
Transabdominal ultrasonography	
Cambridge 0	Normal organ, duct <2 mm, smooth contour
Cambridge 1	Echo-dense organ contour, organ enlarged up to 1.5 times normal size, duct <3 mm, honeycomb-like lobulated texture
Cambridge 2	Irregular contour, irregular echo-dense main duct >3 mm, lobulated texture with echo-dense septa
Cambridge 3	As in 2, with cysts and focal calcifications
Cambridge 4	As in 3, with duct stones, duct obstruction, organ enlarged by tumor to more than twice normal size, splenic vein thrombosis
Endosonography (EUS)	
Cambridge 0	None
Cambridge 1	Honeycomb-like lobulated texture, duct <3 mm
Cambridge 2	Hyperechogenic duct and foci, echo-dense contour, duct <3 mm
Cambridge 3	Honeycomb-like lobulated texture, septated, hyperechogenic foci, duct >3 mm, irregular duct, no duct stones
Cambridge 4	As in 3, with calcifications, duct stones, cysts
Computed tomography / magnetic resonance cholangiopancreatography (MRCP)	
Cambridge 0	None
Cambridge 1	Not identifiable with current CT or MRCP techniques
Cambridge 2	Two or more of the following abnormalities: – pancreatic duct 2 to 4 mm in the body of the pancreas – mild pancreatic enlargement – heterogeneous parenchymal structure – small cysts (<10 mm) – duct irregularities – more than 3 abnormal side branches
Cambridge 3	All the abnormalities listed in 2, above, along with abnormal main duct (>4 mm)
Cambridge 4	One of the abnormalities listed in 2 or 3, above, and one or more of the following: – cystic structures >10 mm – parenchymal calcifications – intraductal filling defects (calcium stones) – duct obstruction (stricture) – major irregularity of duct

Unoperated patients with pancreatic carcinoma have a life expectancy of less than one year; after successful resection, the likelihood of surviving five years is 20% to 25% (25). Symptomatic pseudocysts should be treated. The endoscopic or surgical treatment of a symptomatic pseudocyst is indicated regardless of size (level of evidence: 2a, recommendation grade: B, strong consensus).

Pseudocysts that cause complications such as gastric outlet obstruction, hemorrhage, pain, cholestasis, or vascular stenosis should be treated either endoscopically or surgically. Surgical methods of treating pseudocysts tend to have higher success rates than endoscopic pseudocyst drainage into the duodenum or the stomach but are associated with somewhat higher mortality. (Open surgery [156 cases]: success rate 90%–100%, complication rate 20%, recurrence rate 12%, mortality 5%–20%; laparoscopic surgery [253 cases]: success rate 92%, recurrence rate 3%, complication rate 9%, mortality 0%; endoscopic treatment [1312 cases]: success rate 92%, recurrence rate 8.5%, complication rate 14.4%, mortality <1%) (26).

Asymptomatic pancreatic pseudocysts measuring more than 5 cm in diameter that do not regress within six weeks can be treated (level of evidence: 2a, recommendation grade: C, majority agreement).

In a multivariate analysis, Gouyon showed that pseudocyst size less than 4 cm is the single favorable prognostic factor for spontaneous regression (27). Bradley et al. showed that untreated cysts larger than 5 cm cause complications in 41% of cases (rupture, infection, jaundice, or hemorrhage) (28).

If chronic pancreatitis causes distal bile duct stenosis with cholestasis or jaundice, surgery or endoscopic stenting should be performed. If there are intrapancreatic calcifications, surgery is preferable (level of evidence: 4, recommendation grade: B, consensus).

Cholestasis in chronic pancreatitis can be treated by endoscopic stenting with lasting efficacy over twelve months in only one-third of patients (and in only 9% of those with calcific pancreatitis) (29). If cholangiitis is present, endoscopic drainage should be performed without delay (30). If an indication for surgical treatment is present in a case of chronic pancreatitis with cholestasis, than preoperative endoscopic stenting of the bile duct should be performed only if:

- surgery cannot be performed without delay, or
- cholangiitis is present (level of evidence: 2a, recommendation grade: B, strong consensus).

A study of patients with pancreatic tumors showed that preoperative drainage markedly increases postoperative complications (31).

**The treatment of pain**

The causes of pain in chronic pancreatitis include inflammatory infiltration of the parenchyma and nerve sheaths as well as increased pressure in the pancreatic duct due to stenoses or stones.

The intensity of pain in chronic pancreatitis should be evaluated with a validated pain score such as that of Bloechle et al. or the Visual Analog Scale (VAS) (32) (level of evidence: 1b, recommendation grade: B, strong consensus). The pain of chronic pancreatitis can be treated according to the WHO stepwise algorithm (level of evidence: 5, recommendation grade: D, strong consensus). This is presented in *Table 4*. Surgical treatment is the most effective method of achieving long-term pain relief in chronic pancreatitis (level of evidence: 1a, recommendation grade: A, consensus).

Two randomized controlled trials showed that pancreaticojejunostomy provides better pain relief than endoscopic treatment (Cahen et al.: Bloechle Score 25 [surgery] versus 51 [endoscopy] at 24 months,  $p < 0.001$ ; Dité et al.: pain-free state in 34% of patients after surgery, versus 15% after endoscopic treatment) (23, 24).

### Enzyme supplementation in chronic pancreatitis

Patients who have, or are considered likely to have, steatorrhea (the pathological excretion of more than 15 grams of fat per day in the stool) should receive pancreatin supplementation, as should those with an abnormal pancreatic function test combined with clinical evidence of malabsorption.

Even if the excretion of fat in the stool is in the low abnormal range (7–15 g/d), pancreatin should be given if there is evidence of malassimilation, e.g., weight loss, or if the patient has abdominal manifestations attributable to maldigestion and malabsorption (level of evidence: 1b, recommendation grade: A, strong consensus). Empirical treatment for 4–6 weeks can be useful if symptoms are unclear or equivocal (33).

The dose of pancreatin preparations is expressed in terms of lipase activity. For each of the main meals of the day, 20 000 to 40 000 units (Ph. Eur.) should be given as an initial dose; for lesser amounts of food intake between meals, about 10 000 to 20 000 lipase units can be given (level of evidence: 1b, recommendation grade: B, strong consensus). In case of inadequate efficacy, the enzyme dose should be doubled or trebled (strong consensus, clinical consensus point). If the efficacy remains inadequate, pancreatin granules should be combined with an acid inhibitor (level of evidence: 2b, recommendation grade: B, strong consensus). If this still does not lead to the desired success of treatment, another cause for the persistent symptoms should be sought (strong consensus, clinical consensus point).

Nearly all pancreatic enzyme preparations now available in Germany contain porcine pancreatin. As this is a medication, rather than a food, it may be taken even by patients who choose not to eat pork for religious or ethical reasons (cf. Koran, sura 2, verse 173) (strong consensus, clinical consensus point). The patient should nonetheless be told of the origin of the preparation.

**TABLE 4**

**Recommended analgesic dosages for patients with chronic pancreatitis, according to the guideline of the World Health Organization (38)**

Active substance	Dosage	Type of analgesic
Paracetamol	500–1000 mg bid–tid	peripheral analgesic
Metamizole	500–1000 mg qd–4x/d	peripheral analgesic
Tramadol	100 mg 4x/d, 200 mg extended release bid–tid	low-potency central analgesic (caution: vomiting!)
Tilidine	50–200 mg tid	low-potency central analgesic
Buprenorphine	0.2–0.4 mg tid–4x/d	high-potency central analgesic
Morphine	individual dosing depending on effect	high-potency central analgesic
Levopromazine	10 mg tid–5x/d	phenothiazine neuroleptic
Clomipramine	50–100 mg qd	tricyclic antidepressant

### Surgical techniques and their indications

Surgery is an effective treatment for intractable pain and/or local complications in chronic pancreatitis (24, 34). In principle, endoscopic methods can also be used for these indications; thus, early interdisciplinary discussion is advisable to determine the most appropriate treatment for the individual patient (35). The standard operative technique in chronic pancreatitis with an inflammatory pseudotumor of the head of the pancreas is resection of the head of the pancreas. For this purpose, one of the variants of duodenum-preserving resection of the head of the pancreas (surgery according to Beger, Frey, Bern, Hamburg) or the Kausch-Whipple procedure (either the classic or the pylorus-preserving variant) should be performed (level of evidence: 1a, recommendation grade: A, strong consensus).

If the main problem is an obstructed pancreatic duct, pure drainage procedures such as lateral pancreaticojejunostomy (the Partington-Rochelle procedure) or the Frey operation, with only limited resection of the head of the pancreas, have a good primary success rate. The results are better than those of endoscopic treatment (24, 34), but the long-term success of treatment is still not as good as that obtainable with other techniques in which the head of the pancreas is resected. Moreover, these techniques are likely to succeed only if the ductal system is markedly enlarged (>7 mm) and in the absence of an inflammatory pseudotumor of the pancreatic head (36).

### The monitoring and follow-up of patients with chronic pancreatitis

Chronic pancreatitis gives rise to treatable complications including endocrine and exocrine pancreatic insufficiency, acute episodes of inflammation, pseudocyst formation, cholestasis, and an increased risk of pancreatic carcinoma. Patients should, therefore, have further monitoring and follow-up once the diagnosis has been made (consensus, clinical consensus point).

Twenty years after diagnosis, the mortality of persons with chronic pancreatitis is 38.4% higher than in the general population (3). Clinical experience therefore suggests that follow-up studies should be performed annually (history, physical examination, transabdominal ultrasonography, and laboratory testing including HbA<sub>1c</sub>).

Tumor markers should not be measured as part of the follow-up of patients with chronic pancreatitis (Ca19.9, CEA, or others; level of evidence: 2a, recommendation grade: B, strong consensus).

### The diagnosis and treatment of chronic pancreatitis in childhood

The diagnostic evaluation and treatment of chronic pancreatitis in children and adolescents should be performed under the direction of a pediatric gastroenterologist, in collaboration with an experienced pediatric surgeon or visceral surgeon, a pediatric radiologist, and, where appropriate, an interventional endoscopist (consensus, clinical consensus point).

A sweat test to rule out cystic fibrosis should be part of the etiological work-up of children with chronic pancreatitis (level of evidence: 1c, recommendation grade: A, strong consensus).

Patients with cystic fibrosis with preserved exocrine pancreatic function often suffer from recurrent pancreatitis. Thus, an episode of pancreatitis may, in fact, be the initial manifestation of cystic fibrosis. Moreover, patients with so-called idiopathic chronic pancreatitis often turn out to have mutated CFTR alleles.

#### Conflict of interest statement

Prof. Mayerle has served as a paid consultant for AstraZeneca and has been paid by the Falk Foundation for preparing continuing medical education presentations.

PD Dr. Hoffmeister has received lecture honoraria from the Falk Foundation.

Prof. Lerch has served as a paid consultant for Roche, Abbott, Falk, and Aptalis. He has received reimbursement of scientific meeting participation fees and travel expenses from Roche, Abbott, Menarini, and Falk. He has been paid by Roche, AstraZeneca, Reccordati, Menarini, Abbott, Falk, and Aptalis for preparing continuing medical education presentations. He has received financial support in an external-funding account for conducting clinical trials on behalf of AstraZeneca, Abbott, Menarini, Solvay, Roche, and Sanofi-Aventis. He has also received financial support in an external-funding account from AstraZeneca, Metanomics, Roche, Abbott, Solvay, and SanofiAventis for a research project that he initiated.

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eTables, eBoxes:  
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CLINICAL PRACTICE GUIDELINE

# Chronic Pancreatitis—Definition, Etiology, Investigation and Treatment

Julia Mayerle\*<sup>1</sup>, Albrecht Hoffmeister\*<sup>1</sup>, Jens Werner, Heiko Witt, Markus M. Lerch\*<sup>2</sup>, Joachim Mössner\*<sup>2</sup>

**eTABLE 1**

**Results of the literature search**

19 569 publications 1400 as full text, including 67 RCTs		
WGs	No. of publications	No. of full texts evaluated
WG 1	978	211 full texts on platform
WG 2	1206	227 full texts on platform 191 citations in evidence table
WG 3	954	144 full texts on platform 140 citations in evidence table
WG 4	3615	110 full texts on platform 16 citations in evidence table
WG 5	277	110 full texts on platform 74 citations in evidence table
WG 6	7221	304 full texts on platform 130 citations in evidence table
WG 7	1584	387 full texts on platform 149 citations in evidence table
WG 8	1907	79 full texts on platform 62 citations in evidence table
WG 9	1760	256 full texts on platform 34 citations in evidence table
WG 10	67	21 full texts on platform 20 citations in evidence table

The results of the literature search were critically evaluated in an initial selection phase. Publications whose title or abstract revealed their unsuitability for use in the guideline or inadequate quality were not considered any further (19 569). The full text of the remaining publications was obtained (1400). In order to answer the questions in the preformulated catalogue with evidence of the highest possible level, meta-analyses of randomized controlled trials were sought first, followed by systematic reviews, randomized controlled trials, and lastly observational studies, to answer the questions in each topical area. Evidence was formally classified according to the Oxford scheme (cf. eTable 2). In each working group, the literature was read critically with an evaluation of method and evidence tables were prepared for each publication.

RCT, randomized controlled trial, WG, working group

**eTABLE 2**

**Oxford Centre for Evidence-based Medicine—Levels of Evidence\***

Level of evidence	Description	
Ia	systematic review of randomized controlled trials (RCTs)	
Ib	suitably designed RCT	
Ic	all-or-none principle	
IIa	systematic review of well-designed cohort studies	
IIb	well-designed cohort study or RCT of low quality (e.g., <80% follow-up)	
IIc	outcome research studies	
IIIa	systematic review of well-designed case-control studies	
IIIb	case-control study	
IV	case series, cohort studies, and case-control studies of poor quality	
V	expert opinion without explicit critical evaluation or based on physiological models, laboratory research findings, or "first principles"	

  

Recommendation strength	Formulation of recommendation	Recommendation grade
Strong recommendation	"must"	A
Recommendation	"should"	B
Open recommendation	"can"/"may"	C, D

Negative recommendations are formulated correspondingly.

Consensus strength	Precent agreement among participants
Strong consensus	>95%
Consensus	75–95%
Majority agreement	50–75%
No consensus	<50%

\* As defined by the Oxford Centre of Evidence Based Medicine, www.cebm.net. In the full version of the guideline, evidence levels are reported according to the Oxford scheme. RCT, randomized controlled trial



## eBOX 1

## Specialist society representatives participating in the creation of this guideline

- **The German Association of Digestive and Metabolic Diseases (*Deutsche Gesellschaft für Verdauungs- und Stoffwechselkrankheiten, DGVS*)**
  - Prof. Dr. Markus M. Lerch
  - Prof. Dr. Joachim Mössner
  - PD Dr. Albrecht Hoffmeister
  - Prof. Dr. Julia Mayerle
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  - Prof. Dr. Jakob Izbicki
  - Prof. Dr. Ernst Klar
  - Prof. Dr. Wolfram-T. Knoefel
  - Prof. Dr. Jens Werner
- **The German Society of Internal Medicine (*Deutsche Gesellschaft für Innere Medizin, DGIM*)**
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- **The German Society of Pathology (*Deutsche Gesellschaft für Pathologie, DGP*)**
  - Prof. Dr. Jutta Lüttges
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  - Prof. Dr. Heiko Witt
- **The Austrian Society of Gastroenterology and Hepatology (*Österreichische Gesellschaft für Gastroenterologie und Hepatologie, ÖGGH*)**
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- **The German Pancreas Aid (*Deutsche Pankreashilfe e. V.*)**
  - Dr. rer. nat. Steffen Klabunde
- **The German Radiological Society (*Deutsche Röntgengesellschaft*)**
  - Prof. Dr. Andreas Schreyer
- **The Association of Gastroenterologists in Private Practice (*Berufsverband der niedergelassenen Gastroenterologen, bng*)**
  - Prof. Dr. Jürgen Freise

eBOX 2

**The S3 guideline was created under the aegis of the German Association of Digestive and Metabolic Diseases (*Deutsche Gesellschaft für Verdauungs- und Stoffwechselkrankheiten, DGVS*), in cooperation with:**

● Participating medical societies

- The German Society for General and Visceral Surgery (*Deutsche Gesellschaft für Allgemein- und Viszeralchirurgie, DGAV*)
- The German Society of Internal Medicine (*Deutsche Gesellschaft für Innere Medizin, DGIM*)
- The German Society of Pathology (*Deutsche Gesellschaft für Pathologie, DGP*)
- The German Society of Pediatric Gastroenterology (*Deutsche Gesellschaft für pädiatrische Gastroenterologie, DPGE*)
- The Austrian Society of Gastroenterology and Hepatology (*Österreichische Gesellschaft für Gastroenterologie und Hepatologie, ÖGGH*)
- The Swiss Society of Gastroenterology (*Schweizerische Gesellschaft für Gastroenterologie, SGG*)
- The Swiss Society of Visceral Surgery (*Schweizerische Gesellschaft für Viszeralchirurgie, SGVC*)
- The Association of Pancreatectomized Patients (*Arbeitskreis der Pankreatektomierten e. V.*)
- The German Pancreas Aid (*Deutsche Pankreashilfe e. V.*)
- The German Radiological Society (*Deutsche Röntgengesellschaft*)
- The Association of Gastroenterologists in Private Practice (*Berufsverband der niedergelassenen Gastroenterologen, bng*)

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