

Evidence-based clinical practice guidelines for chronic pancreatitis 2015

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Abstract Chronic pancreatitis is considered to be an irreversible progressive chronic inflammatory disease. The etiology and pathology of chronic pancreatitis are complex; therefore, it is important to correctly understand the stage and pathology and provide appropriate treatment accordingly. The newly revised Clinical Practice Guidelines of Chronic Pancreatitis 2015 consist of four chapters, i.e., diagnosis, staging, treatment, and prognosis, and includes a total of 65 clinical questions. These guidelines have aimed at providing certain directions and clinically practical contents for the management of chronic pancreatitis, preferentially adopting clinically useful articles. These revised guidelines also refer to early chronic pancreatitis based on the Criteria for the Diagnosis of Chronic Pancreatitis 2009. They include such items as health insurance coverage of high-titer lipase preparations and extracorporeal shock wave lithotripsy, new antidiabetic drugs, and the definition of and treatment approach to pancreatic pseudocyst. The accuracy of these guidelines has been

improved by examining and adopting new evidence obtained after the publication of the first edition.

Keywords Chronic pancreatitis · Guidelines · GRADE system · Early stage chronic pancreatitis · Pancreatic exocrine · Pancreatic endocrine · Pancreatic dysfunction · Pain management · Medical conservative therapy · Surgical therapy

Introduction

In Japan, the first edition of the Clinical Practice Guidelines for Chronic Pancreatitis was compiled in 2009, based on the clinical diagnostic criteria for chronic pancreatitis prepared by the Japan Pancreas Society in 2001. However, the 2001 criteria for the diagnosis of chronic pancreatitis were revised to contain the category of early chronic pancreatitis in 2009 [1]. Therefore, in the Clinical Practice Guidelines newly revised in 2015, we have referred to the diagnosis of early phase lesions of chronic pancreatitis based on the Criteria for the Diagnosis of Chronic Pancreatitis 2009; in addition, we have described the advent of high-titer lipase formulations, which have been available in Japan since 2009, and the utility of low-fat elemental diets (ED) for patients with pain. In addition, we have included in these Clinical Practice Guidelines items such as health insurance coverage of extracorporeal shock wave lithotripsy (ESWL), new antidiabetic agents such as incretin-related drugs, and the definition of and treatment approach to pancreatic pseudocyst following the revision of the Atlanta Classification in 2013. We have also added the effects of pancreatic duct stenting on internal pancreatic

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The members of the Guidelines Committee are listed in the [Appendix](#) in the text.

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fistulas with pancreatic ascites and pleural effusions, and biliary stenting on bile duct stenosis complicated by chronic pancreatitis. We aimed at improving the accuracy of these Clinical Practice Guidelines by examining and adopting new evidence obtained after the publication of the first edition of the guidelines. In addition, we have adopted the idea of the GRADE (Grades of Recommendation Assessment, Development, and Evaluation) system in the descriptive content of the statements and determined the degrees of recommendation [2–4]. The revised content of the Clinical Practice Guidelines for Chronic Pancreatitis 2015 consists of four chapters: diagnosis, staging, treatment, and prognosis, and includes a total of 65 clinical questions (CQ). In this article, we will primarily explain the newly revised points described above in the order of the four chapters.

Diagnosis

The definitive diagnosis of chronic pancreatitis is sometimes difficult, especially if the disease is not considered by the physicians treating the patient. This chapter describes how chronic pancreatitis is suspected, based on signs, symptoms, and laboratory results, and how the diagnosis is developed. The CQ are very detailed and consist of 12 items, including history taking, physical examination, determination methods for pancreatic enzymes in the blood and urine [5, 6], significance of various imaging methods [chest and abdominal radiography, abdominal ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), endoscopic ultrasound, and pancreatography] in the diagnosis of chronic pancreatitis [7–15], exocrine pancreatic function testing, pathological diagnosis, differential diagnosis from pancreatic cancer and intraductal papillary mucinous neoplasm (IPMN), and genetic testing [16–20].

In order to facilitate understanding the path to diagnosis, flow diagram 1 (Fig. 1) was prepared. When chronic pancreatitis is suspected, a diagnosis should be made according to the criteria for the diagnosis of chronic pancreatitis revised in 2009 [1]. Definitive and probable diagnosis of chronic pancreatitis can be made by imaging alone. Of the cases in which findings for probable diagnosis are present, those that satisfy two or more items among repeated attacks of upper abdominal pain, abnormalities in blood/urine pancreatic enzymes, and exocrine pancreatic dysfunction are definitively diagnosed as chronic pancreatitis. However, the concept of early chronic pancreatitis has been adopted. Cases that do not qualify for definitive or probable diagnosis but which satisfy two or more items from the above three findings in addition to persistent drinking history (80 g/day), and show appropriate imaging findings as well (Table 1), are diagnosed as early chronic pancreatitis.

Staging

Chronic pancreatitis generally first presents with repeated upper abdominal and back pain, and endocrine and exocrine pancreatic function gradually deteriorates [21, 22]. In Japan, the disease is classified into three phases: compensated, transitional, and uncompensated, depending on the stage; however, an early chronic pancreatitis category has been added before the compensated phase in this revision [1]. Exocrine pancreatic disorder (that includes digestive and absorptive disorders) and abnormal glucose tolerance (pancreatic diabetes) occur as chronic pancreatitis progresses; therefore, to improve prognosis, pharmacological and nutritional therapies should be given in accordance with the stage of the disease. In this regard, staging of chronic pancreatitis is important. The CQ in this chapter comprise eight items, and clinical signs, blood and urine pancreatic enzyme levels, imaging, exocrine pancreatic function tests, and abnormal glucose tolerance tests, as well as the significance of scoring of these factors, are all important in determining the severity, staging, and treatment of chronic pancreatitis [23–32].

Treatment

There are numerous CQ in the Clinical Practice Guidelines for Chronic Pancreatitis. This chapter comprises six items (treatment strategy, lifestyle guidance, pain management, treatment of exocrine pancreatic insufficiency, treatment of diabetes mellitus, and treatment of complications), and there are CQ for each of these items. The treatment strategies and contents differ depending on the severity and the stage of chronic pancreatitis; in addition, surgical treatment sometimes becomes necessary. Flow diagram 2 (Fig. 2) shows the outline of the treatment path, flow diagram 3 (Fig. 3) shows the path of conservative medical treatment, and flow diagram 4 (Fig. 4) shows the path of surgical treatment.

Treatment strategy

Treatment strategies are individually explained according to causes, presence or absence of activity, severity, and stage; in addition, items such as whether the treatment strategies for chronic pancreatitis differ depending on lifestyle, especially alcohol drinking habits, are also discussed.

- The etiology and pathology of chronic pancreatitis are complex, and the treatment differs depending on individual stages. In Japan, chronic pancreatitis is classified into compensated, transitional, and uncompensated phases. Exocrine pancreatic disorder (that

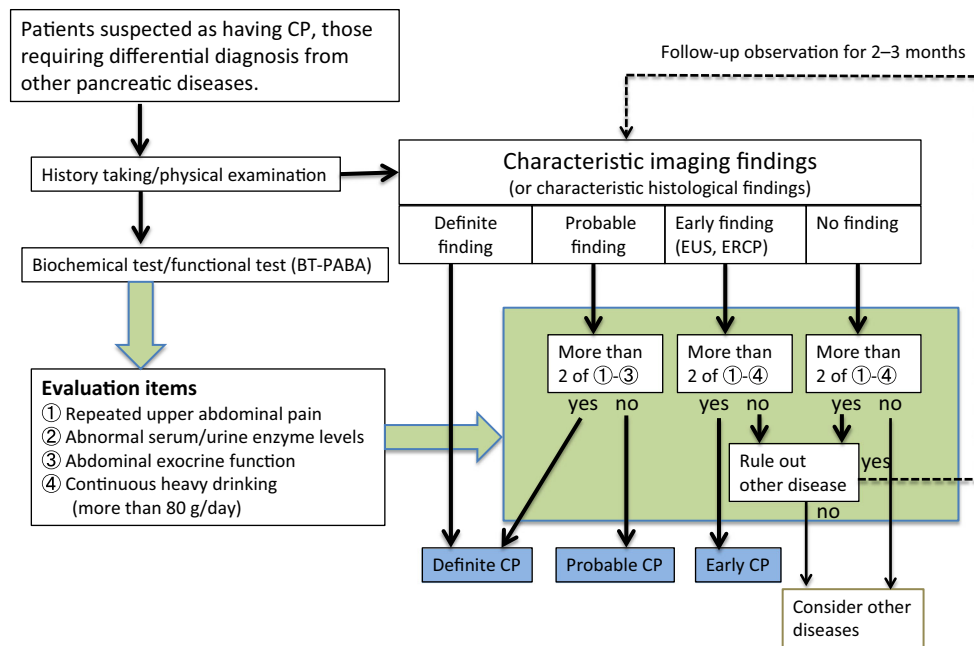


Fig. 1 Diagnostic path for chronic pancreatitis. The figure shows a schematic flow diagram for the diagnosis of chronic pancreatitis (CP). EUS endoscopic ultrasonography, ERCP endoscopic retrograde cholangiopancreatography

Table 1 Imaging findings of early chronic pancreatitis (either a or b)

- (a) More than two among the following seven features of EUS findings including at least one of (1–4)
 1. Lobularity with honeycombing
 2. Lobularity without honeycombing
 3. Hyperechoic foci without shadowing
 4. Stranding
 5. Cysts
 6. Dilated side branches
 7. Hyperechoic MPD margin
- (b) Irregular dilatation of more than three duct branches on ERCP

EUS endoscopic ultrasonography, MPD main pancreatic duct, ERCP endoscopic retrograde cholangiopancreatography

includes digestive and absorptive disorders) and abnormal glucose tolerance (pancreatic diabetes) occur as chronic pancreatitis progresses; therefore, to improve prognosis, pharmacological and nutritional therapies should be given in accordance with the stage of the disease [33–35].

- In the compensated phase, the prevention of repeated relapses and pain has priority; therefore, diet therapy to avoid excessive pancreatic stimulation and pharmacotherapy with mainly protease inhibitors are important. However, in the uncompensated phase, marked digestive and absorptive disorders appear. Pancreatitis symptoms such as upper abdominal and back pain often remit or disappear; therefore, the loss of fat in stool should be considered, and physicians should not

uniformly direct patients to take low-fat meals. Steatorrhea is gauged by making patients take a sufficient amount of fat (50–70 g/day), followed by administration of a sufficient amount of digestive enzyme preparations. With the availability of pancrelipase, a high-titer digestive enzyme preparation, oral administration of small numbers or amounts of capsules or granules has become possible [36–39]. In addition, in the uncompensated phase, the secretion of bicarbonate, which maintains an alkaline pancreatic juice, is dramatically reduced; therefore, the pH of the upper small intestine is decreased. When postprandial pH in the small intestine becomes 4 or lower, the bile acids precipitate and digestive enzymes (lipases in particular) lose their activities; therefore, poor digestion and absorption of fat ensue. For patients with steatorrhea due to exocrine pancreatic dysfunction, in order to increase the pH in the upper small intestine, concomitant administration of antacids such as H₂ receptor antagonists and proton pump inhibitors with digestive enzyme preparations becomes necessary [40–43].

- In the uncompensated phase, which involves digestive and absorptive disorders (exocrine pancreatic insufficiency) due to pancreatic dysfunction-induced insufficient pancreatic secretion, it is important to control digestive and absorptive disorders and pancreatic diabetes. Therefore, in order to avoid poor nutritional conditions, an appropriate amount of fat should be given to patients, followed by administration of a

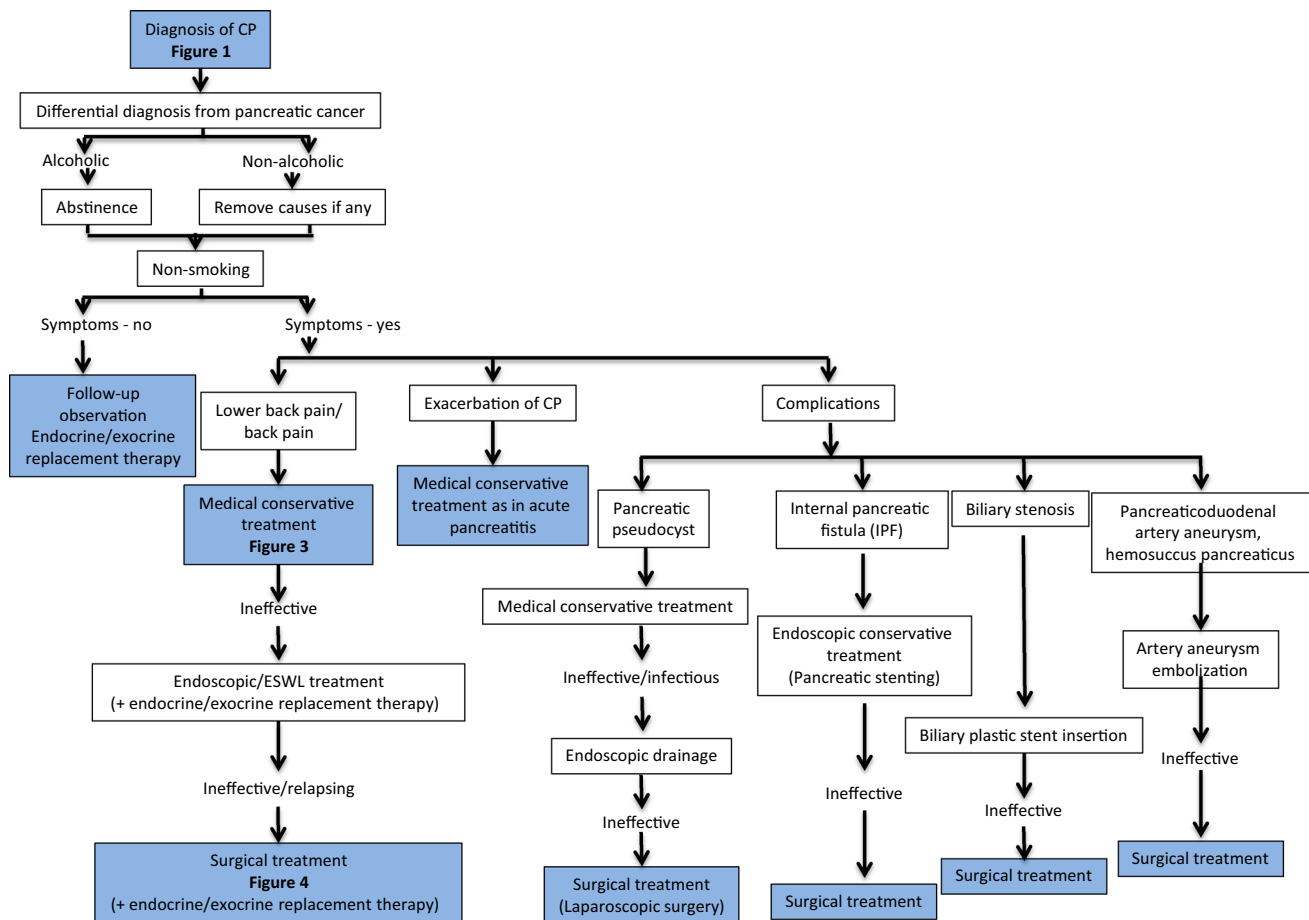


Fig. 2 Therapeutic path for chronic pancreatitis. The figure shows a schematic flow diagram for the therapy of chronic pancreatitis (CP)

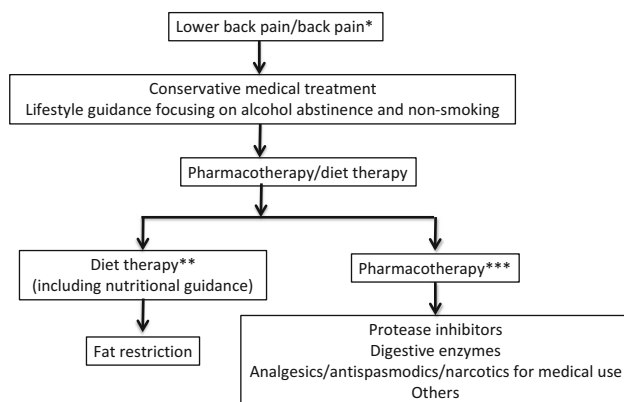


Fig. 3 Conservative medical treatment path for chronic pancreatitis. The figure shows a schematic flow diagram for the conservative medical treatment of chronic pancreatitis (CP). *Single asterisk* with regard to cases of acute exacerbation of chronic pancreatitis, severity diagnosis for acute pancreatitis should be made promptly and treatment strategy in accordance with that for acute pancreatitis should be determined. *Double asterisks* therapy with an elemental diet may be considered. *Triple asterisks* in pharmacotherapy, choice of drug and selection of dose should be decided according to this figure

sufficient amount of digestive enzyme preparations. For diabetes mellitus, it is necessary to control blood glucose and to determine the amount of insulin to be administered [44, 45].

- Incretins [glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP)], which are hormones secreted by the digestive tract, dependently promote insulin secretion and glucose-concentration; in addition, they are known to have protective and proliferative effects on pancreatic beta cells. Recently, drugs targeting these incretins, i.e., GLP-1 agonists and inhibitors of the incretin-degrading enzyme, dipeptidyl peptidase-4 (DPP-4), have been developed and have drawn attention as new treatments for type 2 diabetes mellitus [46]. On the other hand, the utility of incretin-related drugs for pancreatic diabetes mellitus has not yet been established. In these guidelines, we have proposed the use of these drugs only when the benefits of treatment are considered to surpass the risks. In addition, sodium/glucose cotransporter 2

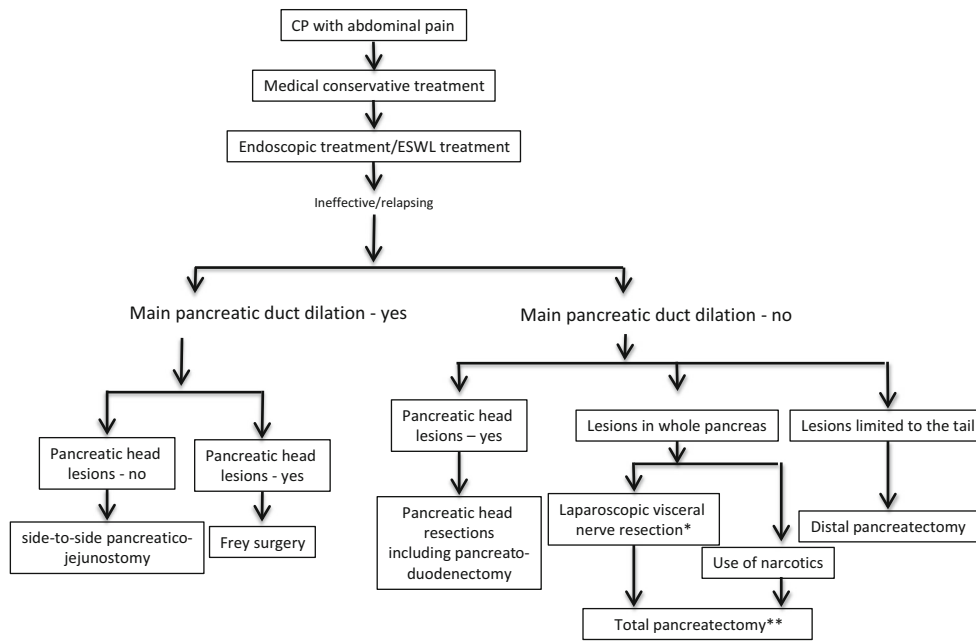


Fig. 4 Surgical treatment path for chronic pancreatitis. The figure shows a schematic flow diagram for the surgical treatment of chronic pancreatitis (CP). *Single asterisk* efficacy may be expected only for pain involving sympathomimetic nerves. Treatment strategy

(SGLT2) inhibitors have been newly developed; however, as in the case of incretin-related drugs, no evidence showing efficacy against diabetes mellitus complicated by chronic pancreatitis has been observed [47–50].

- In chronic pancreatitis, various complications occur. These include pancreatic pseudocyst, pancreatic abscess, internal pancreatic fistulas with pancreatic ascites and pleural effusions, biliary stenosis, and hemosuccus pancreaticus. These guidelines discuss pharmacotherapy, endoscopic treatment, and surgical treatment for the above complications. In addition, ESWL has become covered by health insurance and reimbursable in Japan. Endoscopic treatment including ESWL is effective against abdominal pain due to chronic pancreatitis and thus is recommended in these guidelines. In addition, pancreatic stenting, which was shown to be effective for abdominal pain, has also become reimbursable by insurance. However, the criterion for the duration of pancreatic stent treatment has been set at approximately 1 year. In ineffective or relapsing cases, a proposal to consider surgical treatment has been made [51–62].

Lifestyle guidance

If the cause of chronic pancreatitis is alcoholic, abstinence from alcohol is necessary. These guidelines explain how to

should be decided after explaining the possible use of narcotics and associated risks. *Double asterisks* this applies only in cases in which strict postoperative lifestyle guidance, including abstinence from alcohol drinking, is possible

guide patients to abstinence using a flow diagram [63–65]. In addition, smoking increases the risks of developing chronic pancreatitis and pancreatic calcification. Abstinence from smoking may prevent the progression of chronic pancreatitis; therefore, giving smoking cessation guidance is recommended [66–68].

Pain management

Abdominal and back pain are major contributors to deterioration of the quality of life of patients with chronic pancreatitis. Inability to lead a social life, worsening nutritional conditions because of inability to ingest food, etc., are grave concerns that often confront practicing physicians. These guidelines refer to various pharmacotherapies and also describe the application of endoscopic and surgical treatments [69–71]. The utility of an elemental diet (ED) in patients with chronic pancreatitis with pain has been demonstrated; therefore, ED is recommended in these guidelines. Among various enteral nutrients, Elental, an ED, is characterized by its extremely low fat content and is reimbursable by health insurance for use for pancreatic diseases [72]. In these guidelines, fat-restricted diet therapy is considered basic for patients with chronic pancreatitis who present with attacks of abdominal pain; therefore, restriction of dietary fat is proposed for the management of abdominal pain.

Prognosis

Generally, chronic pancreatitis is a progressive inflammatory disease. Therefore, staging and determination of severity are necessary during follow-up observation; in other words, observation and evaluation of clinical symptoms, such as abdominal pain, changes of pancreatic enzyme levels over time, morphology of the pancreas, and endocrine and exocrine pancreatic functions, are useful. In addition, patients with chronic pancreatitis constitute a high-risk group for ordinary-type pancreatic cancer [73–75]. Although clear evidence for testing is lacking, many patients with chronic pancreatitis lead a lifestyle associated with carcinogenic risks (alcohol drinking and/or smoking), and it is useful to perform cancer screening [65, 76–81].

Conclusions

The Clinical Practice Guidelines for Chronic Pancreatitis 2015 describe general principles regarding the diagnosis, treatment, and prognosis of chronic pancreatitis and thus support decision-making by practicing physicians. These guidelines may be used by general clinicians, but in the following cases, referral to a pancreatologist is recommended: (1) chronic pancreatitis with repeated attacks of acute pancreatitis; (2) chronic pancreatitis in which pain and nutritional management is difficult; (3) chronic pancreatitis with pancreatic diabetes mellitus in which glucose control is difficult; (4) familial/hereditary and juvenile-onset chronic pancreatitis; and (5) chronic pancreatitis with advanced complications/comorbidities.

Chronic pancreatitis has a prolonged course; therefore, even if the drugs or treatments remain the same, their method of use may need to be changed, depending on the stage of the disease. In these guidelines, efforts have been made to promote visual understanding of the overall flow: we have prepared flow diagrams for general diagnosis and treatment, conservative medical treatment, and surgical treatment; we have also created CQ that correspond to the individual items above to enhance understanding.

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Compliance with ethical standards

Conflict of interest Any financial relationship with enterprises, businesses, or academic institutions in the subject matter or materials discussed in the manuscript are listed as follows: (1) those from which the authors, the spouse, partner or immediate relatives of the authors, have received individually any income, honoraria or any other types of remuneration; no conflict of interest; and (2) those from which the academic institutions of the authors received support (commercial/academic cooperation); Astellas Pharma Inc., AstraZeneca K.K.,

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Appendix

Members of the Guidelines Committee who created and evaluated the JSGE “Evidence-based clinical guidelines for chronic pancreatitis” are listed below.

Executive Committee

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