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SPECIAL ARTICLE

Evidence-based clinical practice guidelines for functional dyspepsia

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Abstract General interest in functional gastrointestinal disorders is increasing among Japanese doctors as well as patients. This increase can be attributed to a number of factors, including recent increased interest in quality of life and advances in our understanding of the pathophysiology of gastrointestinal disease. Japan recently became the world's first country to list "functional dyspepsia" as a disease name for national insurance billing purposes. However, recognition and understanding of functional dyspepsia (FD) remain poor, and no standard treatment strategy has yet been established. Accordingly, the Japanese Society of Gastroenterology (JSGE) developed an evidence-based clinical practice guideline for FD, consisting of five sections: concept, definition, and epidemiology; pathophysiology; diagnosis; treatment; and prognosis and complications. This article summarizes the Japanese guideline, with particular focus on the treatment section. Once a patient is diagnosed with FD, the doctor should carefully explain the pathophysiology and benign nature of this condition, establish a good doctor–patient relationship, and then provide advice for daily living (diet and lifestyle modifications, explanations, and reassurance). The proposed pharmacological treatment is divided into two steps: initial treatment including an acid inhibitory drug (H2RA or PPI) or prokinetics, (strong recommendation); second-line treatment including anxiolytics, antidepressants, and Japanese traditional medicine (weak recommendation). *H. pylori* eradication, strongly recommended with a high evidence level, is positioned separately from other treatment flows. Conditions that do not respond to these treatment regimens are regarded as refractory FD. Patients will be further examined for other organic disorders or will be referred to specialists using other approaches such as psychosomatic treatment.

Keywords Dyspepsia · Guideline · Proton pump inhibitor · Prokinetics · Antianxiety drug · Antidepressant · Japanese traditional medicine · *H. pylori* eradication treatment · *H. pylori* associated dyspepsia · Algorithm · Chronic gastritis

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The members of the Working Committee are listed in the Appendix in the text.

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Introduction

Up to this point, Japanese advances in gastroenterology have focused primarily on the morphological characteristics of organic gastrointestinal disease, while functional gastrointestinal disorder has received relatively little attention. However, today we are seeing a sharp rise in the awareness of functional gastrointestinal disorder. This is attributable in part to increased concerns about quality of life, associated with the improved standards of living in Japan. An additional

contributing factor may be stress, which has increased with the growing complexity of modern life.

Abdominal complaints account for a large percentage of visits to general practitioners in Japan. Clearly, these patients need accurate diagnosis and science-based treatment. In response to this need, the Japanese Society of Gastroenterology (JSGE) has created evidence-based guidelines for the standard diagnosis and treatment of functional gastrointestinal disorders.

The JSGE divided functional gastrointestinal disorder into the two categories of functional dyspepsia and irritable bowel syndrome, and created and evaluated guidelines based on the GRADE (grading of recommendations assessment, development, and evaluation) system. The members of the guideline-creating committee and the guideline-evaluating committee were appointed with consideration of recommendations from the Japanese Gastroenterological Association and the Japanese Society of Neurogastroenterology. The committees began work on the guidelines in July of 2011. After the clinical questions were created, a list of keywords based on those questions was formulated, and the literature was searched. The committee members began writing the statements and commentary in April 2013. Each candidate statement was discussed and voted on, and the statements and commentaries were decided. Those statements and commentaries were then evaluated and revised by the evaluation committee. Following a period for public comment, the materials underwent final revision. The "Evidence-based clinical practice guidelines for functional dyspepsia" were completed in February 2014, and were published in April of that year.

The treatment of functional dyspepsia in Japan is characterized as follows. First, Japanese physicians have a low level of awareness of functional gastrointestinal disorder. Because of the high prevalence of gastric cancer in Japan, great emphasis has been placed on the importance of early diagnosis and treatment of gastric cancer, and as a result, the Japanese population has excellent access to endoscopic testing. However, conditions other than organic disease tend to be viewed as "nothing to worry about." In part, this is because conditions with fairly good life prognosis naturally tend to be considered less seriously. In addition, until recently functional dyspepsia was not listed as a disease name used for national insurance billing purposes, so functional dyspepsia could be confused with chronic gastritis. To remedy this, the authors of the new guidelines worked to clearly distinguish between functional dyspepsia and chronic gastritis in the definitions and epidemiology sections.

Second, because of the universal health insurance system, Japanese people have excellent access to medical centers, and symptomatic patients tend to visit a medical center soon after symptoms develop. Because gastric cancer screening tests and comprehensive physical examinations are so widely available in Japan, endoscopic examination seldom shows organic disease such as gastric cancer or ulcer in patients who complain of dyspepsia. The Rome III criteria define "chronic" as "symptoms for the last 3 months with symptom onset at least 6 months prior to diagnosis." However, this definition clearly does not apply in Japan, because symptomatic patients will generally not wait for 3 months before seeing a doctor. These guidelines thus use a broader definition.

Third, Japan has a high level of awareness of *Helicobacter pylori* (*H. pylori*) infection, not only among researchers but also among ordinary family physicians. In February 2013, Japanese national health insurance added coverage of eradication therapy in patients with *H. pylori* gastritis. However, not all dyspepsia responds to *H. pylori* eradication. Physicians need to understand the relationship between *H. pylori* and dyspepsia from a scientific perspective, and then to implement a strategy that gives priority to the eradication of *H. pylori*. These guidelines consider *H. pylori* eradication therapy separately from other treatment options for functional dyspepsia, and at the same time provide an algorithm that recommends eradication.

Fourth, a wide range of prokinetics are available for use in Japan; acotiamide joined the list of available products in May 2013. Chinese herbal (Kampo) medicines are also widely used. Reliable evidence is available for the use of acotiamide, and prokinetics are positioned as first-choice drugs under the algorithms that have been developed.

Also of importance in this context, "functional dyspepsia" is now listed as a disease name for national insurance billing purposes. Japan was the first country in the world to provide this recognition of functional dyspepsia for national insurance billing purposes, as of May 2013. However, at present acotiamide is the only drug whose indications include this disease name. When the use of acotiamide is controlled by insurance, it will hinder physicians' ability to use the drug as they see fit in ordinary clinical practice. As a result, the guidelines have been shifted away from insurance-approved treatment, and evidence-based algorithms have been developed.

These guidelines lay the groundwork for consistently accurate diagnosis and science-based treatment of patients with functional dyspepsia. Because of the high prevalence of functional dyspepsia in Japanese patients, this condition has considerable clinical importance in Japan. Such patients need diagnosis and treatment that follow a science-based medical treatment plan. The completion of these evidence-based treatment guidelines for functional dyspepsia is thus of considerable significance.

Of final note, these guidelines are written for the physicians who must diagnose and treat patients with functional dyspepsia. All funding for guideline preparation was provided by the JSGE.

Algorithm

Figure 1 shows algorithms for the diagnosis and treatment of functional dyspepsia (FD). The algorithms are based on the consensus opinion of the members of the guideline-creating committee and the guideline-evaluating committee, and take into consideration statements prepared using the GRADE method.

The treatment of FD can differ depending on the situation; for example, a gastrointestinal (GI) specialist may have access to endoscopic procedures which a primary care physician does not. Two different algorithms have thus been provided for these specific situations. The third algorithm is a simplified version for all settings.

Initial treatment is divided into a first step and a second step. Initially, the first-step medication is administered. If that treatment is ineffective, then the second-step medication is substituted or added to the treatment protocol. First-step medications have grade 1 recommendation with evidence level A, and consist of acid reducers and agents to improve gastric motility. Second-step medications have grade 2 recommendation with evidence level A, and include anxiolytics, antidepressants, and traditional (Japanese herbal) medicines.

A GI specialist will also recommend that *H. pylori*-positive patients undergo early eradication therapy. Those patients who test negative for *H. pylori* after eradication therapy, but continue to experience dyspepsia, will receive routine FD treatment. Patients who remain symptom-free 6–12 months after eradication are considered to be cases of "*H. pylori*-associated FD." If symptoms remain unchanged after initial treatment, the condition is classified as refractory FD, and the patient is tested for organic disease or referred to a specialist for treatment. Such treatment can include autogenic training, cognition behavioral therapy, and hypnotherapy.

These diagnostic options are summarized in Table 1.

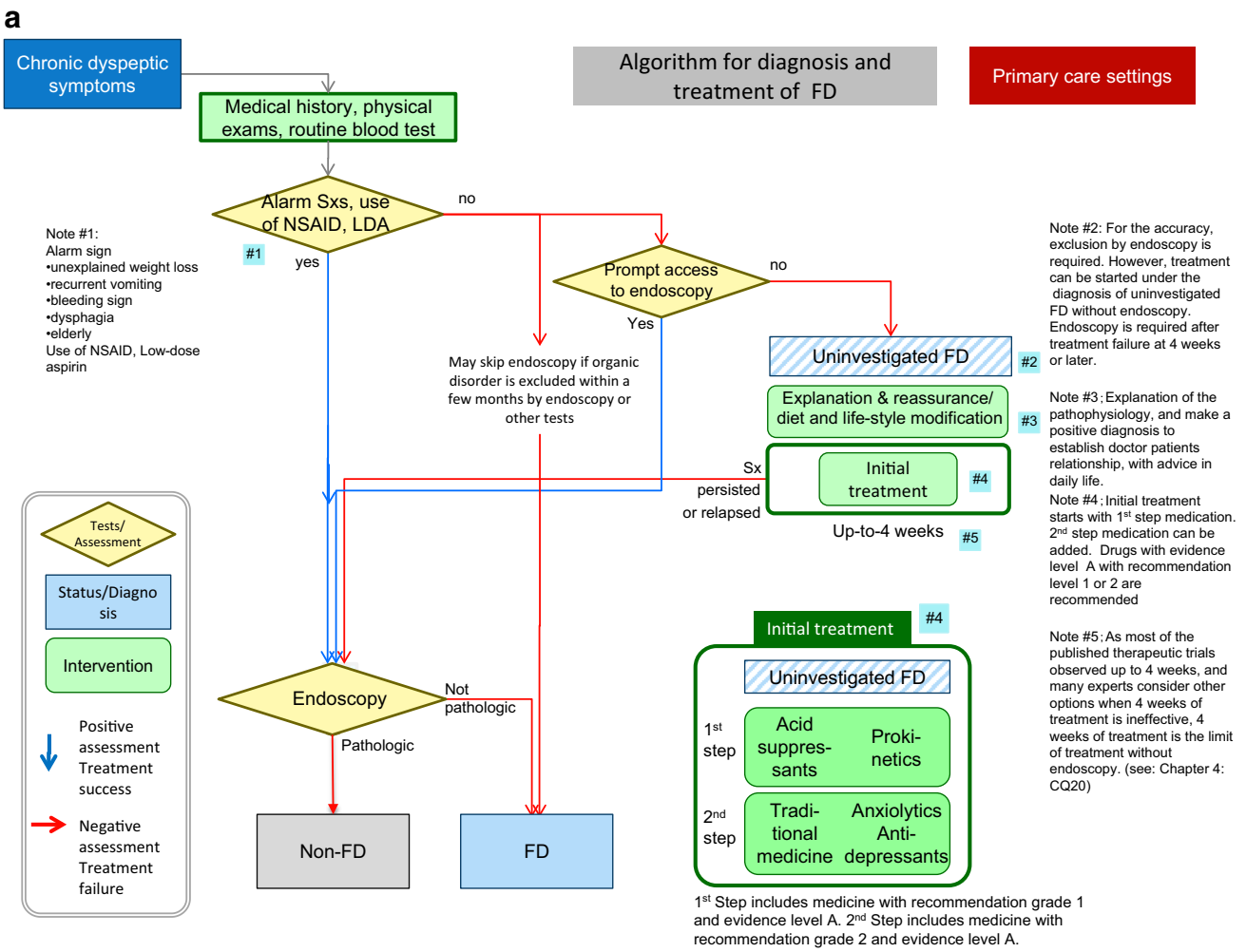

Fig. 1 Algorithms for the diagnosis and treatment of functional dyspepsia (FD) for use **a** in primary care settings, **b** by GI specialists, and **c** all settings (a simplified version)

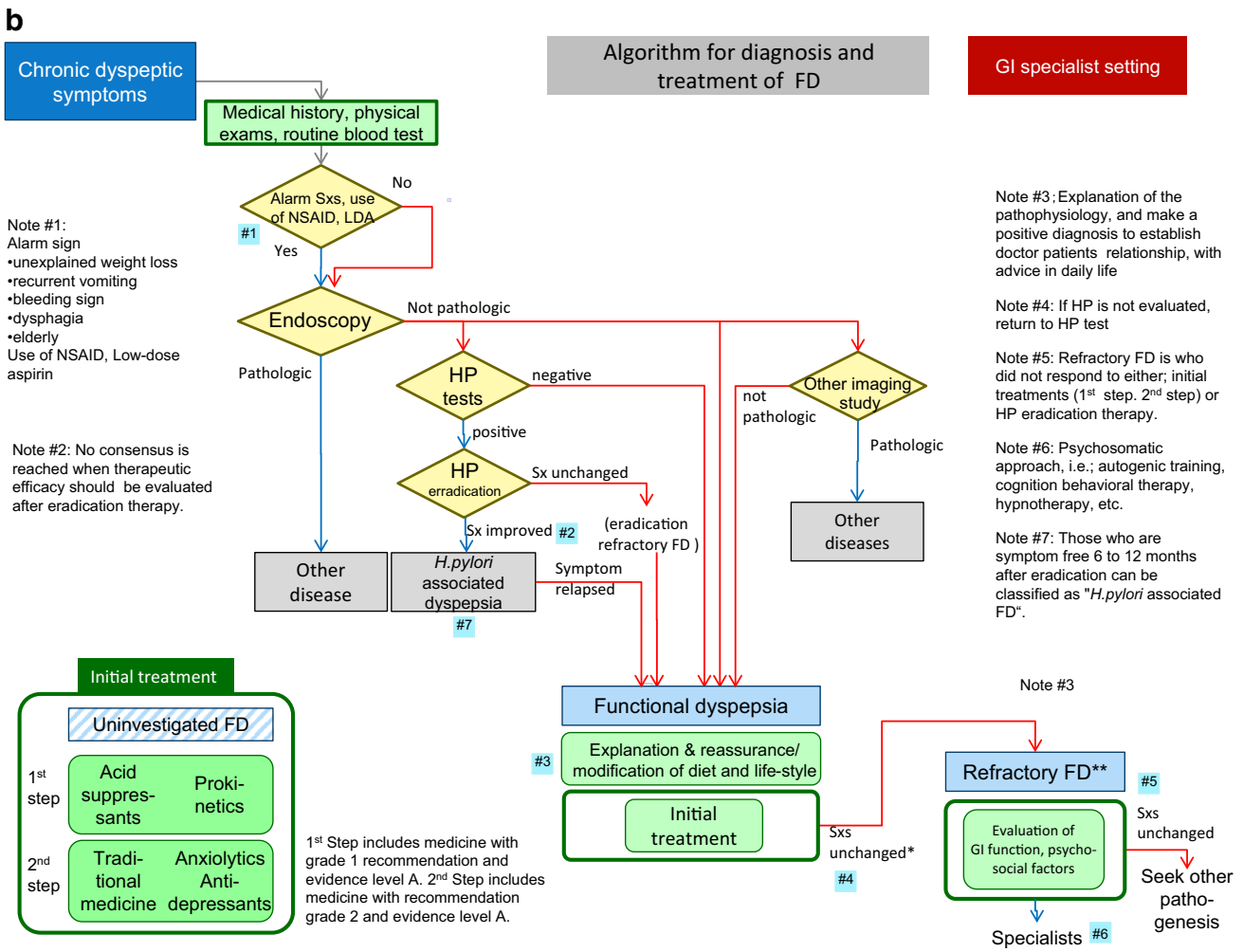

Fig. 1 continued

Definition and epidemiology

Dyspepsia, functional dyspepsia, chronic gastritis

- Dyspepsia refers to symptoms centered in the upper abdomen, such as epigastric pain or discomfort.
- Functional dyspepsia (FD) is defined as a condition chronically presenting symptoms centered in the upper abdomen, such as epigastric pain or discomfort, in the absence of any organic, systemic, or metabolic disease that is likely to explain the symptoms.
- Many FD patients have been treated as having chronic gastritis. However, these conditions are different. FD is defined by symptoms.
- The Rome III definition for FD is not necessarily applicable in a Japanese clinical setting.

Comment: The term "dyspepsia" came originally from Greek, and had the meaning of "bad (dys) digestion (peptein)". However, today the term no longer carries the meaning of "bad digestion," but instead has become a medical term for abdominal symptoms centered primarily in the epigastric region.

In the past, dyspepsia included conditions such as heartburn. However, today those conditions are generally attributed to reflux and are considered to be an esophageal symptom, so they are no longer included in the dyspepsia category.

Dyspepsia can have various causes, including organic conditions such as gastric ulcer and cancer. However, many dyspepsia patients remain symptomatic in the absence of obvious organic disease. The term "functional dyspepsia" (FD) is used for those patients. The new guidelines define the condition as "symptoms of chronic dyspepsia in the absence of underlying organic, systemic, or metabolic disease that explains those symptoms."

At present the Rome III criteria, for application in clinical research, are widely used around the world. Those criteria require the presence of at least one of the following four conditions: postprandial fullness, early satiation, epigastric pain, and epigastric burning. The condition must

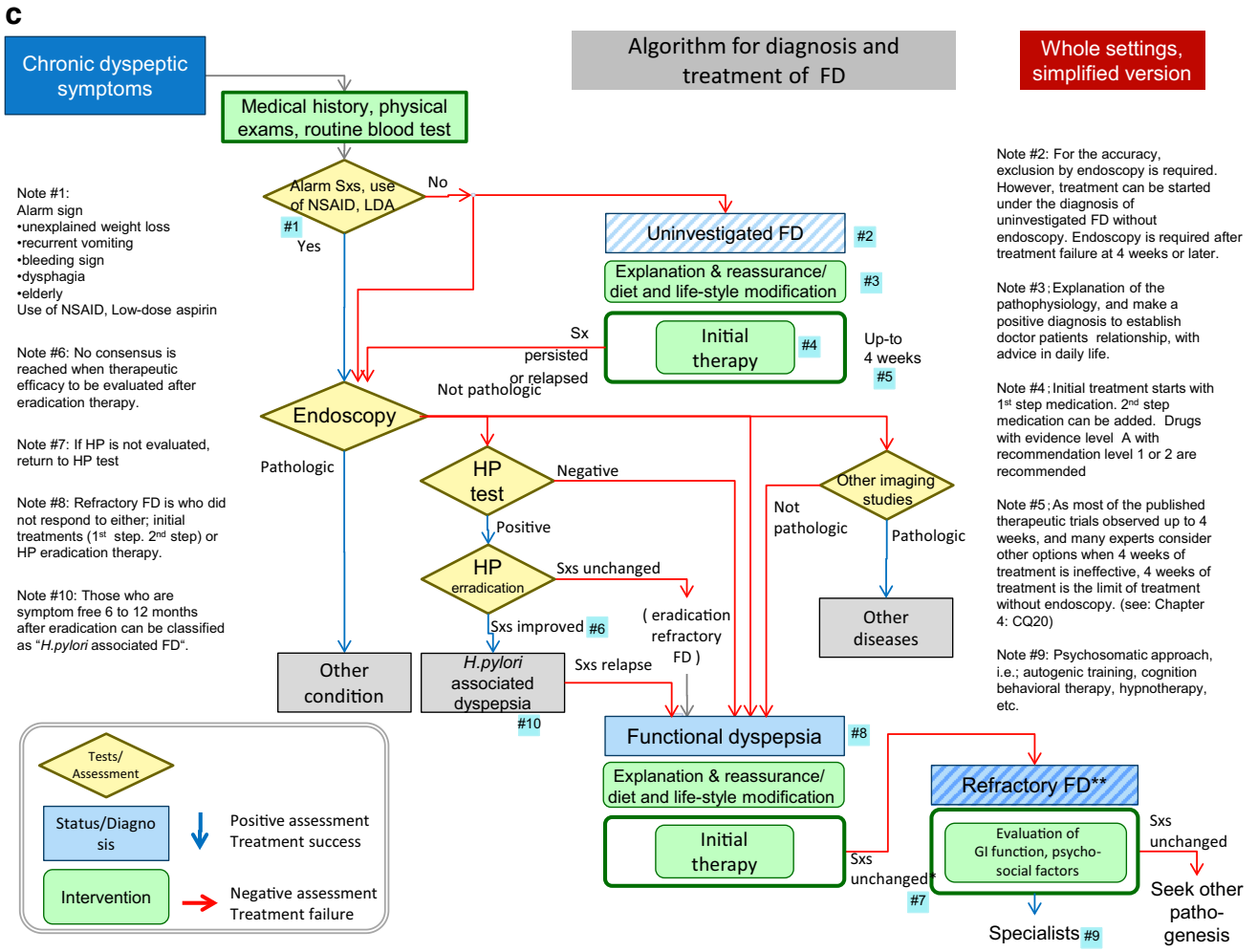

Fig. 1 continued

have persisted for at least 3 months, and the initial symptoms must have appeared at least 6 months previously [1]. However, perhaps because almost all Japanese people have health insurance coverage, patients generally visit a medical facility within a month of symptom onset. As a result, most Japanese patients do not meet the Rome III criteria for duration of symptoms (onset at least 6 months previously and symptoms persisting for at least 3 months) and therefore cannot be diagnosed with functional dyspepsia under those criteria [2, 3].

The new Japanese guidelines contain a general definition, and rely on the clinical physician to decide whether the patient's symptoms qualify as dyspepsia and whether those symptoms are chronic. Until recently, most functional dyspepsia patients in Japan have been diagnosed with and treated for chronic gastritis. However, chronic gastritis intrinsically involves histological inflammation of the gastric mucosa, and the diagnosis is unaffected by the presence or absence of symptoms. Gastritis is thus in a completely different diagnostic class from functional dyspepsia, which is diagnosed from symptoms. The use of these two very different names for the diagnosis of the two conditions should help to reduce confusion.

Prevalence of FD

- The prevalence of functional dyspepsia in Japanese patients ranges from 11 to 17 % in subjects who have medical checkups and from 45 to 53 % in patients who seek medical care because of upper gastrointestinal symptoms.
- Because of the absence of reliable data, it is difficult to determine whether the prevalence of Japanese patients with functional dyspepsia is increasing.

Comment: Although results for the prevalence of FD in Japanese patients varied according to the definition used in each research project, differences were not significant (Table 2) [4–10]. An epidemiological study on the prevalence of FD in Western countries showed findings of 14.7 % in North Europe, 15 % in the USA, and 23.8 % in the UK [11]. These results suggest that the prevalence of

Table 1 Diagnostic tests used to diagnose FD depending on the level of clinical practice

	CQ	Grade	EvL	PCP	GI specialists	Research institute
History taking (Medical interview)				●	●	●
Self-administered questionnaire	2-2	na		△	△	△
Physical examination	2-7	na		●	●	●
Inquire use of NSAID, LDA	2-9	na		●	●	●
CBC & blood biochemistry	2-7	na		●	●	●
Serology for Inflammation	2-7	na		●	●	●
Fecal occult blood	2-7	na		●	●	●
Abdominal XP	2-2	na		●	●	●
EGD	2-1	2	B	△	●	●
H.pylori test	2-6	1	A	△	●	●
Ba swallows 視	2-2	na		△	△	●
Abdonimal US study	2-2	na		△	△	●
Abdominal CT scans	2-2	na			△	●
GI function tests**	2-2	na				●
Evaluation of psycho-social factors	2-5	1	C	△	△	●

EvL: evidence level
na: not available
LDA: low dose aspirin

PCP: Primary Care Physician
△: Perform if possible
●: Recommend to perform
*: Modalities may vary depend on institutions

Table 2 The reported prevalence of FD in Japanese patients

References	Years	Study design	Definition of FD	Subjects	Number	Prevalence (%)
Kinoshita [4]	1992	Cross-sectional study	NUD (AGA working group)	Outpatients	106	53
Schlemper et al. [5]	1993	Cross-sectional study	NUD (AGA working group)	Medical checkup	731	13
Hirakawa et al. [6]	1999	Cross-sectional study	NUD (AGA working group)	Medical checkup	1,139	17
Kawamura et al. [7]	2000	Cross-sectional study	Rome criteria (1991)	Medical checkup	907	11
Kawamura et al. [8]	2001	Cross-sectional study	Rome II	Medical checkup	2,263	
				Dysmotility		8.9
				Ulcer-like		5.2
Kaji et al. [9]	2010	Cross-sectional study	Rome III	Medical checkup	2,680	10
Okumura et al. [10]	2010	Cross-sectional study	Rome III (partially modified)	Outpatients	381	44.6

NUD non-ulcer dyspepsia, *AGA* American Gastroenterological Association

FD in Japan is lower than in the West. Only limited data are available on changes in HD prevalence, although risk factors for FD seem to be increasing.

Gender, BMI, age, and FD

- Women are reported to be more prone to FD than men, although only limited data are available in Japan.
- The relationship between FD prevalence and body mass index remains highly controversial.
- Many data suggest that FD is more prevalent in younger persons than in the elderly, although these findings remain controversial in Japan.

Comment: Considerable epidemiological data are available about gender, obesity, age, and FD [12, 13], although those data have been reported primarily from Western countries. In addition, unfortunately, inconsistent results have been obtained on the relationship between the prevalence of FD and body mass index (BMI) because different criteria were used for FD. Furthermore, FD is a multifactorial disease, so results could also be influenced by factors other than BMI, including sociopsychological stress. In addition, differences still remain between Japan and Western countries with regard to several environmental factors, including lifestyle and diet, so data from Western countries are not always applicable to Japanese FD patients.

Consultation behavior

- Patient behavior with regard to first clinic visit is not influenced by the duration of FD, but resistance to return visits is related to the duration of symptoms.

Comment: Patient consultation behavior with regard to the first clinic visit is determined not only by the patient's quality of life but also by personality, mental state, and health insurance status. Two studies from Japan suggested that patient behavior with regard to the first clinic visit was not influenced by the duration of FD [2, 3]. In an earlier European study, FD patients from Denmark, France, Germany, Netherlands, Hungary, and Poland were followed up for 3 months after a 4-week treatment trial with proton pump inhibitors or placebo. Results from that study revealed that symptom resolution in FD patients had a positive impact on quality of life and reduced subsequent costs for a 3-month period after cessation of initial treatment because the patient resisted returning to the clinic [14]. Those findings suggest that FD patients are more likely to return to the clinic if their FD symptoms continue despite treatment.

Quality of life in FD

- FD patients have impaired quality of life.
- The intensity of FD symptoms is related to the extent of impairment of quality of life.
- The duration of FD is not always related to the extent of impairment of quality of life.

Comment: There have been many studies to evaluate the quality of life (QOL) in FD patients by using several kinds of QOL assessment tools, with consistent results [9, 15, 16]. Several studies have also shown a clear correlation between severity of symptoms and negative impact on QOL. The clinical course of FD is not well known, but interestingly, there have been reports of some FD patients whose symptoms resolved naturally in a clinical situation. Although the available data remain insufficient, two recent studies have indicated that the duration of FD is not related to the extent of impairment of QOL [2, 17]. Accordingly, since the current data are inconclusive, this statement notes that QOL is not always related to the duration of FD.

Pathophysiology

Gastric motility abnormality and visceral hypersensitivity

- Multiple factors seem to be involved in the pathogenesis of FD.
- Disturbance of gastric accommodation is involved in the pathogenesis of FD.
- Disturbance of gastric emptying is involved in the pathogenesis of FD.
- Since hypersensitivity has been demonstrated by stimulation through gastric distention and infusions of acid and lipid into the duodenum, visceral hypersensitivity is involved in the pathogenesis of FD.

Comment: Multiple factors may be associated with the pathophysiology of functional dyspepsia. These factors can include impaired gastric accommodation, delayed gastric emptying, hypersensitivity, social factors, *H. pylori* infection, gastric acid secretion, genetic factors, psychological factors (anxiety or history of abuse), history of infectious colitis, lifestyle (including alcohol consumption and smoking), and morphology of the stomach (cascade stomach).

Both impaired gastric accommodation and delayed gastric emptying are classified as gastric motility abnormality. A close relationship has been reported between symptoms and impaired gastric accommodation, although full consensus has not yet been reached. Recently, results from a randomized, double-blind, placebo-controlled study showed a close relationship between restoration of impaired gastric accommodation and symptomatic relief [18]. Several reports suggest that gastric emptying is impaired in some FD patients, and a meta-analysis indicates that gastric emptying is significantly delayed in almost 40 % of patients with FD [19]. Most studies failed to find a convincing relationship between delayed gastric emptying and symptom pattern, and some studies reported rapid gastric emptying after meals [20] in some FD patients. Visceral hypersensitivity is also regarded as a pathophysiologic factor, and hypersensitivity has been reported to gastric distension [21] and to acid and fat infusion to the duodenum [22].

Psychosocial factors and acid

- Psychosocial factors contribute to symptoms in FD.
- The presence of gastric acid is thought to be a cause of FD, because dyspeptic symptoms can be reduced by acid blockers and because acid affects gastrointestinal motility and sensitivity.

Comment: FD patients scored higher than average for psychosocial factors, and major anxiety was significantly associated with FD and postprandial distress syndrome (PDS) in patients. Findings from a meta-analysis showed a moderate correlation between non-ulcer dyspepsia and depression and anxiety, and the non-ulcer dyspepsia group had significantly more frequent episodes of depression and anxiety disorder than the control group [23]. In population-

based studies, anxiety disorder was the condition most strongly associated with gastrointestinal symptoms [24].

The efficacy of acid blockers for dyspeptic symptoms has been demonstrated in a few meta-analyses [25]. Additionally, acid infusion into the stomach has been reported to induce dysmotility-like predominantly dyspeptic symptoms in healthy Japanese control subjects [26]. Duodenal acidification induces proximal gastric relaxation, increases sensitivity to gastric distension, and inhibits gastric accommodation during and immediately after a meal [27]. These findings suggest that acid plays a role in the pathogenesis of functional dyspepsia.

H. pylori infection

- Since eradication treatment for *H. pylori* improves dyspeptic symptoms in a subset of FD patients, there is a relationship between *H. pylori* infection and FD.

Comment: There is room for argument about the relationship between *H. pylori* infection and functional dyspepsia. Although *H. pylori* infection induces chronic inflammation and changes mucosal morphology and the function of acid secretion, the effects of *H. pylori* on gastric motility and sensation remain unclear. However, a systematic review of randomized controlled trials revealed a 10 % relative risk reduction in the *H. pylori* eradication group compared to the placebo group [28]. Therefore, *H. pylori* infection is associated with pathogenesis in a subset of functional dyspepsia. A global consensus on *H. pylori*-associated dyspepsia is under discussion. Patients whose dyspeptic symptoms are improved by *H. pylori* eradication should not be diagnosed with functional dyspepsia [29] and this condition may be labeled as *H. pylori*-associated dyspepsia.

Genetics and early life events

- There is a possibility that family history and genetic polymorphisms are associated with FD.
- In some cases, a history of abuse in childhood and/or adolescence is associated with FD.

Comment: An association has been reported between the development of functional dyspepsia, family history, and genetic polymorphisms such as C825T of G-protein beta3, T1675C of cyclooxygenase-1, and G315C of TRPV1 [30, 31]. A relationship between functional dyspepsia and a history of abuse in childhood and adolescence has also been reported.

Postinfectious FD

- FD following acute gastroenteritis is also observed in Japan.

Comment: In some cases of infectious gastroenteritis accompanied by fever, diarrhea, nausea, vomiting, and positive stool culture, studies have shown that FD symptoms persist long after the elimination of the causative pathogens [32, 33]. Postinfectious FD is associated with early satiety, weight loss, and nausea [34]. Infiltration by duodenal inflammatory cells such as eosinophils, mast cells, and macrophages may play an important role in the pathophysiology of postinfectious FD patients [33].

Other pathophysiological factors of FD

- Smoking, alcohol intake, and sleep disorders are associated with symptoms of FD.
- Intake of a high-fat diet aggravates clinical symptoms of FD.
- Cascade stomach is associated with dyspeptic symptoms.

Comment: Some studies have reported that smoking aggravates FD symptoms and that alcohol intake and sleep disorders are associated with FD symptoms in Japanese populations [35, 36]. A previous study reported that high fat intake induces nausea and abdominal pain in FD patients compared to healthy volunteers [37]. High fat intake was also reported to be associated with abdominal fullness in FD patients. Although FD patients have a tendency to consume less fat during the day, there is a significant increase in their intake of fat at night. The consumption of spicy foods and capsaicin also affects FD symptoms [38]. Poor eating habits, such as skipping breakfast or lunch and snacking while performing other tasks, could be involved in the symptomatology of FD. The shape of the stomach is considered to be a risk factor in the pathophysiology of FD patients, and cascade stomach is reported to be associated with FD symptoms [39].

Diagnosis

Diagnostic modalities for FD

- Since FD is a diagnosis of exclusion, upper endoscopy should be considered for patients during the clinical course. [Recommendation 2 (100 %), evidence level B].
- Imaging modalities other than endoscopy are recommended for diagnosis of FD. [Recommendation 2 (90 %), evidence level C].

Comment: A diagnosis of FD is established by evaluation of symptoms and exclusion of organic disease, including gastric cancer. Endoscopy is recommended for exclusion of organic dyspepsia because symptomatic criteria do not

distinguish between functional and organic dyspepsia [40]. However, endoscopic examination is not available in some primary clinical settings, so we made endoscopy a level 2 recommendation. This allows patients in those settings to be treated initially without endoscopy (see algorithm for primary care setting).

Imaging modalities including ultrasonography and scintigraphy are useful not only for providing an excluded diagnosis of organic dyspepsia, but also for evaluation of gastrointestinal function [41, 42]. However, assessment of gastrointestinal functionality using imaging modalities is not covered by national health insurance, and is not strongly recommended.

Biomarkers

- At present, there are no clinically useful biomarkers for the diagnosis of FD.

Comment: Many biomarkers, including plasma ghrelin and several gene polymorphisms [43], have been reported to play a role in the pathophysiology of FD. However, most of them are not practical for use except in highly specialized centers, or do not constitute a sufficiently accurate predictor of the diagnosis of FD.

A self-reporting questionnaire

- A self-reporting questionnaire is useful for symptom assessment and is necessary for the management of FD patients. [Recommendation 2 (100 %), evidence level B].

Comment: There are many self-reporting questionnaires, including the GSRS [44] and the Izumo scale [45], which are often used in Japan as well as overseas. These questionnaires are very useful not only for the diagnosis of FD but for the evaluation of treatment efficacy in FD.

Evaluation of psychosocial factors and *H. pylori* infection

- The evaluation of psychosocial factors is recommended for the management of FD patients. [Recommendation 1 (100 %), evidence level C].
- Assessment of *H. pylori* infection is recommended for the diagnosis of FD. [Recommendation 1 (100 %), evidence level A].

Comment: Psychosocial factors have been proposed as an element in the pathophysiology of FD; there seems to be a relationship between anxiety, depression, and FD. It is important to evaluate these factors in clinical practice, and psychosomatic intervention including stress management may be necessary in both the diagnosis and the treatment of FD patients.

Many studies have investigated the association between *H. pylori* infection and dyspeptic symptoms or pathophysiologic mechanisms in FD. However, the effect of *H. pylori* infection on FD remains controversial, and the role of *H. pylori* eradication in FD patients is still uncertain. The US guidelines for the management of dyspepsia recommend *H. pylori* eradication for *H. pylori*-positive FD patients. It is at least necessary to assess *H. pylori* infection in the management of FD patients.

Alarm signs

- An alarm sign is considered to be any sign that raises suspicion of an organic disease. [Recommendation 2 (100 %), evidence level B].

Comment: No difference in the incidence of alarm signs has been reported between organic diseases and FD [46]. If an alarm sign is noted, organic disease should be suspected. However, the absence of alarm signs does not exclude the possibility of organic disease.

Gastrointestinal function testing

- Gastrointestinal function testing is not widely available, and the test results do not necessarily agree with pathogenesis or improve the therapeutic predictability of functional gastrointestinal disorders. The usefulness of such testing in clinical practice thus remains unclear at present.

Comment: In a subset of patients, gastrointestinal function testing could identify symptom-generating pathogenesis such as disorders of gastric emptying or gastric accommodation, and could provide useful information for selection of the best therapeutic option. However, such testing is only performed at specialized medical centers.

NSAIDs, LDA, and FD

- A diagnosis of FD is excluded if the patient is using NSAIDs or low-dose aspirin (LDA) and the symptoms are reduced or eliminated when that use is discontinued.

Comment: Findings from a meta-analysis showed significantly increased prevalence of dyspeptic symptoms after NSAID administration [47]. Patients who are taking NSAIDs or LDA should not be diagnosed with FD.

Evaluation of the severity of FD

- Findings from a questionnaire to evaluate disease severity may predict therapeutic response and potential improvement in QOL.

Comment: The evaluation of symptom severity, based on findings from a patient questionnaire, could predict therapeutic resistance [48] and QOL [49].

Treatment

General concept of the treatment of FD

- To obtain the satisfactory relief of symptoms is an important objective in the treatment of FD. [Recommendation NA, evidence level B].
- Placebo may have a profound effect on the treatment of FD. [Recommendation NA, evidence level A].
- The efficacy of placebo does not differ between men and women. [Recommendation NA, evidence level C].
- Building a favorable patient–doctor relationship is effective for controlling symptoms in patients with FD. [Recommendation 1 (100 %), evidence level B].
- Lifestyle guidance and dietary treatment are effective for FD. [Recommendation 1 (100 %), evidence level B].

Comment: "Satisfactory or adequate relief of symptoms" has been used as an acceptable primary endpoint in several clinical trials to treat patients with functional gastrointestinal disorders [50], and has also served as a useful endpoint in a clinical trial to treat patients with FD [51].

The placebo effect is known to be larger for FD than for other organic diseases of the gastrointestinal tract. One report showed that the mean placebo effect in the treatment of FD was approximately 56 %, but other reports cited a wide range (5–90 %) [25]. Research also suggests that the effect of a placebo appears to be greater for FD than for Crohn's disease (18 %) and ulcerative colitis (9.1 %) [52, 53]. In particular, a full explanation of FD, including the unlikelihood of cancer, may relieve FD patients and result in symptomatic improvement, which in turn may contribute to and increase the placebo effect.

Two cohort studies using the data from placebo arms in double-blinded, placebo-controlled studies showed no gender-based differences in placebo response. Reported factors of lower placebo response rate include a consistent predominant symptom pattern, lower body mass index, and smoking [54, 55]. The importance of building a favorable patient–doctor relationship for treating patients with functional gastrointestinal disorder has been described in Rome III [56] and has been acknowledged by several experts [57]. This relationship is an undoubted fundamental in medicine. It is also likely that changes in lifestyle and dietary habits can be useful in the management of FD. Pilichiewicz et al. [37] suggested the possibility that the FD symptoms in part might be diminished by avoiding a high fat diet. FD patients may tend to avoid eating properly [36], and may benefit from lifestyle guidance and dietary treatment. The Rome III criteria also describe the usefulness of dietary treatment.

First-line treatment of FD

- Acid suppressants are effective for the treatment of patients with FD. [Recommendation 1 (91 %), evidence level A].
- Proton pump inhibitors (PPIs) and histamine type 2 receptor antagonists (H2RAs) provide the same level of efficacy, and both are effective for the treatment of FD. [Recommendation NA, evidence level A].
- Prokinetics are effective for controlling symptoms in patients with FD. [Recommendation 1 (91 %), evidence level A].
- *H. pylori* eradication therapy is effective for a subgroup of *H. pylori*-positive FD patients. [Recommendation 1 (91 %), evidence level A].

Comment: The Cochrane database systematic review in 2006 showed the response rate for H2RA to be 22 % over placebo and PPIs to be 14 % over placebo in patients with non-ulcer dyspepsia. However, there are few reports of acid suppressants in the treatment of patients with FD as diagnosed by the Rome III criteria. Further studies will be needed using Rome III criteria, though these meta-analyses suggest that acid suppressants are effective for the treatment of patients with FD. The Cochrane review concluded that there were no differences in the effects of PPI and H2RA [25]. However, no clinical trials have assessed that difference using the Rome III criteria.

Some meta-analyses have reported the usefulness of prokinetics, although effectiveness has been somewhat inconsistent. Several prokinetics are available in Japan. Of those, only acotiamide, a kind of anticholinesterase inhibitor, has been approved by Japanese health insurance for the treatment of meal-related symptoms of FD. The effectiveness of acotiamide over placebo has been proven in several randomized controlled trials (RCTs) conducted under good clinical practice (GCP) guidelines [36, 58].

A study of *H. pylori* infection, including patients who met the Rome III criteria, demonstrated that symptoms were improved by eradication therapy [59]. And one single-arm short-term study in patients who met Rome III criteria demonstrated that efficacy of eradication therapy was recognized only for epigastric pain syndrome and not

for postprandial distress syndrome [60]. The recent systematic review showed that eradication therapy provided a small but significant improvement in symptoms; those findings were consistent with previous systematic reviews [61]. Since there is no "heroic drug" for FD as of yet, eradication therapy provides a useful treatment option even though its effect is small.

As noted above, these two drugs (either acid suppressants or prokinetics) are recommended as first-line treatment for FD. Eradication therapy for *H. pylori* infection should also be regarded as first-line treatment. However, because this treatment is recommended for all infected subjects, even if they are asymptomatic, we have positioned it separately in the treatment algorithm.

Second-line treatment of FD

- Some herbal medicines are effective for the treatment of patients with FD. [Recommendation 2 (100 %), evidence level A].
- Some antidepressants and anxiolytics are effective for the treatment of patients with FD. [Recommendation 2 (100 %), evidence level A].

Comment: There is some evidence for the therapeutic efficacy of Rikkunshito, a Japanese herbal medicine, for improving gastrointestinal motility disorders in the treatment of FD. Recently, a review article described the basic science and clinical evidence for such use, and discussed future applications for various kampo medicines in the treatment of gastrointestinal tract disorders [62].

In Japan, an RCT was done on the efficacy of tandospirone citrate (a 5-HT1A agonist) in improving symptoms of patients with FD [63]. In addition, two meta-analyses have shown the efficacy of antidepressants and anxiolytics in the treatment of FD patients [64, 65]. However, as of this writing only a few reports describe large-scale randomized clinical trials using these psychiatric drugs for FD.

As noted above, these drugs (antidepressants, anxiolytics, and some herbal medicines) should be used for the second-line treatment of FD if first-line therapy fails to cure or improve dyspeptic symptoms.

Alternative or complementary therapy for FD

- The efficacy of antacids, prostaglandin analogues (misoprostol), and gastroprotective agents (sucralfate and rebamipide) for the treatment of FD has not been proven. [Recommendation NA, evidence level B].
- Combination drug therapy is sometimes performed to control symptoms in patients with FD, although supportive data are lacking. [Recommendation NA, evidence level NA].
- Cognition behavior therapy is effective for controlling symptoms in patients with FD. [Recommendation 2 (100 %), evidence level B].
- There is no definitive evidence about the efficacy of autogenic training for the autonomic nervous system in the treatment of patients with FD. [Recommendation NA, evidence level NA].
- Hypnotherapy is effective for FD, and is recommended. [Recommendation 2 (100 %), evidence level B].
- The efficacy of transcutaneous electroacupuncture has been reported but not confirmed. There have been no clinical trials on the effect of moxibustion. [Recommendation NA, evidence level D].

Comment: The Cochrane review noted no effect from prostaglandin analogues and gastroprotective agents [25]. After that review, the efficacy of rebamipide was assessed in double-blinded, placebo-controlled studies. However, one study from the USA was terminated before it reached the planned sample size [66], and one study from Japan showed no effect [67], suggesting that the effectiveness of these drugs is not yet clear. Combination drug therapy is sometimes performed to control symptoms in patients with FD in clinical practice, but there is little evidence of usefulness. Since the pathophysiology of FD is multifaceted, combination therapy with drugs that target different causes might be effective. Further study is needed on this issue.

A randomized clinical trial showed that cognition behavior therapy was effective in patients with FD, but the sample size was relatively small [68], and other information on this issue is limited. A few cross-sectional and case–control studies have been conducted on the association between imbalance of the autonomic nervous system and the pathogenesis of FD [69, 70]. However, no efficacy has been proven, either for the drugs described above or for autogenic training for autonomic nervous system intervention. Few studies confirm the effectiveness of hypnotherapy, although their results suggest that hypnotherapy may be more effective than drug therapy for the treatment of FD [71]. One study showed the efficacy of transcutaneous electroacupuncture in the treatment of FD [72], but in another study the results of classical six-point manual acupuncture could not be differentiated from the placebo [73]. Neither transcutaneous electroacupuncture nor manual acupuncture is widely practiced in Japan, and no studies have been reported.

If the above recommended first-line and second-line regimens are unsuccessful, FD patients may undergo alternative or complementary therapies as a further step in the treatment regimen. However, little definitive evidence is available in Japan on such therapies, and their efficacy has not been established thus far.

Other statements

- Treatment of FD based on its subtypes of the Rome III criteria may be appropriate. [Recommendation 2 (90 %), evidence level A].
- Whether or not patients who suffer from dyspeptic symptoms for years are resistant to FD treatment is still unclear. [Recommendation NA, evidence level NA].
- The recommendation period to change the treatment for refractory FD is around 4 weeks. [Recommendation 2 (70 %), evidence level C].
- Drug treatment can be ceased after the disappearance of symptoms. [Recommendation 2 (80 %), evidence level C].

Comment: FD is usually diagnosed according to the Rome III criteria, and most clinical trials using any drugs such as acid suppressants and prokinetics are often performed after clinical subclassification according to the Rome III criteria. Therefore, treatment of FD based on its subtypes as described in the Rome III criteria may be appropriate, even though earlier reports indicate some controversy over the clinical significance of such subtype classification. A previous study suggested that the effect of FD treatment was decreased with increasing duration of dyspeptic symptoms [74], while another study reported no correlation between the effects of FD treatment and duration of dyspeptic symptoms [14]. Clearly consensus has not yet been achieved regarding the relationship between effects of FD treatment and duration of symptoms.

The guidelines for FD in both the Asia–Pacific region and the USA recommend changing to a different drug if adequate therapeutic efficacy has not been achieved after 4 weeks of treatment [75, 76]. And around 70 % of clinical trials in patients with FD have used 4 weeks as the period for evaluating therapeutic efficacy of the drug [75]. The Design of Treatment Trials Committee of the European Medicines Agency (EMEA) has approved a 4-week treatment period for evaluating the therapeutic efficacy of a drug in patients with functional gastrointestinal disorders [50]. Cessation of drug treatment may be associated with recurrence of symptoms at various rates [14, 77, 78]. However, there have been no reports of disadvantages due to the cessation of drug treatment after symptom resolution. Therefore, it may be sufficient to restart drug treatment after the recurrence of symptoms.

Prognosis and complications

- FD may be recurrent.
- FD may be associated with mood disturbances or neurotic disorders.
- The prevalence of overlap between FD and gastroesophageal reflux disease (GERD) is relatively high.
- The prevalence of overlap between FD and irritable bowel syndrome (IBS) is relatively high.
- The concurrence of FD and chronic constipation may be high.
- Chronic pancreatitis may not be completely excluded in patients with FD.

Comment: There are reports indicating the recurrence of FD. Three months after 4-week PPI treatment, approximately 20 % of treated FD patients had a recurrence [14]. Similarly, 6 months after *H. pylori* eradication, approximately 27 % of the treated FD patients had a recurrence [79].

Some previous studies have suggested that psychological problems are more commonly seen in FD patients than in patients with peptic ulcer disease and healthy controls [80, 81], but another study indicates that psychological problems in FD patients occurred at the same frequency as in healthy individuals [82]. A meta-analysis based on studies that were performed up to 2001 suggested that there was no significant difference in the ratios of affective disorders and neurotic disorders between FD patients and healthy individuals [23]. However studies that were published after the meta-analysis have led to the above statement, i.e., that FD may be associated with mood disturbance or neurotic disorders [83, 84]. In addition, be careful not to diagnose patients suffering from depression and somatization disorder as FD, because such patients sometimes complain of symptoms similar to digestive symptoms without reporting symptoms of depression and somatization disorder.

There are reports showing the prevalence of overlap between FD and GERD. According to those reports, 25 % of FD patients also show GERD symptoms [9]. Thus, such overlap will almost certainly be encountered by physicians in a clinical setting. There are also reports of prevalence overlap between FD and IBS. According to those reports, overall 30–60 % of FD patients also experience IBS [85]. That overlap will also be encountered in a clinical setting, in particular by physicians who act as consultants for FD patients.

Constipation, of undefined duration, was more prevalent in patients with FD than in patients with GERD and organic upper gastrointestinal disease [86], although there are no reports showing a correlation between FD and chronic constipation.

A subset of dyspeptic patients has reduced pancreatic function; one report suggests that chronic pancreatitis may be present in 24.1 % (111/460) of dyspeptic patients without a previous diagnosis of chronic pancreatitis [87]. No reports are available regarding the relationship between

FD and functional gallbladder and sphincter of Oddi disorders, or between FD and pancreatic cancer.

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Appendix

Members of the Working Committee who created and evaluated the JSGE "Evidence-based clinical guidelines for functional dyspepsia" are listed below.

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Naomi Uemura (National Center for Global Health and Medicine).

The Japanese Society of Gastroenterology

President, Tooru Shimosegawa (Division of Gastroenterology, Tohoku University Graduate School of Medicine); Former President, Kentaro Sugano (Jichi Medical University).

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