

# SECTION I: FGIDs: BACKGROUND INFORMATION

## Functional Gastrointestinal Disorders: History, Pathophysiology, Clinical Features, and Rome IV



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Functional gastrointestinal disorders (FGIDs), the most common diagnoses in gastroenterology, are recognized by morphologic and physiological abnormalities that often occur in combination including motility disturbance, visceral hypersensitivity, altered mucosal and immune function, altered gut microbiota, and altered central nervous system processing. Research on these gut-brain interaction disorders is based on using specific diagnostic criteria. The Rome Foundation has played a pivotal role in creating diagnostic criteria, thus operationalizing the dissemination of new knowledge in the field of FGIDs. Rome IV is a compendium of the knowledge accumulated since Rome III was published 10 years ago. It improves upon Rome III by: (1) updating the basic and clinical literature; (2) offering new information on gut microenvironment, gut-brain interactions, pharmacogenomics, biopsychosocial, gender and cross-cultural understandings of FGIDs; (3) reduces the use of imprecise and occasionally stigmatizing terms when possible; (4) uses updated diagnostic algorithms; and (5) incorporates information on the patient illness experience, and physiological subgroups or biomarkers that might lead to more targeted treatment. This introductory article sets the stage for the remaining 17 articles that follow and offers a historical overview of the FGID field, differentiates FGIDs from motility and structural disorders, discusses the changes from Rome III, reviews the Rome committee process, provides a biopsychosocial pathophysiological conceptualization of FGIDs, and offers an approach to patient care.

**Keywords:** Functional GI Disorders; Rome Foundation; Rome Criteria; History; Biopsychosocial Model; Neurogastroenterology; Patient Provider Relationship; Rome IV; Classification; Diagnosis; Treatment Approach.

Although descriptions of functional gastrointestinal symptoms have been noted for centuries, the functional gastrointestinal disorders (FGIDs) emerged only over the past several decades. Our conceptual understanding of their origins and clinical features evolved from a dualistic and reductive perspective to a more comprehensive biopsychosocial model,<sup>1,2</sup> and the scientific bases for symptom generation changed from being disorders of motility to the more inclusive disturbances of neurogastroenterology and brain-gut interactions.<sup>3</sup> This evolution has legitimized FGIDs to patients and health care providers and nurtured the science to better characterize these disorders and produce new drug discoveries and treatments.

The Rome Foundation has its origins in the late 1980s, at a time when there was little understanding of the pathophysiology of FGIDs, no established classification system, and no guidelines for standardized research of the patients. Subsequently, the Foundation has played a pivotal role in operationalizing the research and disseminating the knowledge surrounding these disorders. Also, by gathering experts from around the world who use more positive parameters for diagnosis and perform fewer studies to exclude other disease, the Rome Foundation identifies experts who are in the best position to provide guidelines for diagnosis and treatment.

### History of the Functional Gastrointestinal Symptoms and Disorders and the Role of Psychosocial Factors

Throughout recorded history, the bowels and intestinal activity have had meanings that go beyond their actual function. They usually are considered private and shrouded in mystery. Their dysfunction is linked to embarrassment, emotion, and shame, and proper bowel functioning is thought to be required for general well-being. We also recognize bowel function and dysfunction as being related closely to stress and emotion: “I find this hard to swallow,” “I cannot stomach that any longer,” and “I feel butterflies in my stomach.” Conversely, and likely as evolving for health benefit, intestinal contents and feces are noxious to the senses; the sight, smell, and touch of these can lead to avoidant emotional responses, nausea, and vomiting. Thus, brain and gut more than any other organ systems are hardwired; each has a nervous system that is linked and derived from the same anlage, the embryonic neural crest.

This brain-gut connection also explains why stress and psychological factors are linked so closely to gut function and dysfunction, gastrointestinal symptoms, illness, and disease. Understanding how these factors relate to one another has evolved from the changing mores, belief systems, or explanatory (folk) models of the time. Explanatory models of

**Abbreviations used in this paper:** CNS, central nervous system; FGID, functional gastrointestinal disorder; GI, gastrointestinal; IBS, irritable bowel syndrome; SOD, sphincter of Oddi.

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illness and disease arise and change in response to new technologies and the need for clinical solutions; however, new models require acceptance by society based on theories that may have existed for centuries and across cultures. Thus, the perception of symptoms may be considered problems in one population, but ignored in another. This perception can occur simply based on prevalence, in that symptoms that are more common would be considered normal. For example, among lower socioeconomic Mexican Americans in the Southwest, diarrhea is common and is not usually perceived as an illness requiring health care seeking,<sup>4</sup> whereas in other sectors of society, diarrhea is considered an illness to be investigated or treated.

Another important influencing factor for a symptom to be perceived as an illness relates to its congruence with dominant or major value orientations: that is, how it is recognized by the society. In some nonliterate societies, the description of hallucinations is accepted with interest, possibly indicating specialness, having magical powers, or connecting with spiritual beings. However, in Western society, the admission of a hallucination would be considered a potentially serious medical problem possibly caused by psychosis or drug toxicity.<sup>5</sup> Societal and cultural values also can affect even the development or nondevelopment of symptoms. Margaret Mead noted that nausea, which is a common and acceptable part of pregnancy in the West, does not occur among the Arapesh of New Guinea, because there is denial that a child exists until shortly before birth.<sup>6</sup> The following section traces cultural influences on research and knowledge of gastrointestinal symptoms and illness, consequently leading to the identification and categorization of functional gastrointestinal (GI) disorders.

### *Antiquity Through the Late 19th Century: Holism and Cartesian Dualism*

The possibility that passions or emotions could lead to the development of medical disease was first proposed by the Greek physician Claudius Galen and has been upheld by medical writers into the 21st century. This supposition is not surprising because we observe the effects of intense emotion on autonomic arousal, leading to diarrhea, the production of chest or abdominal pain, or even sudden death.<sup>7</sup> Even today, when the pathophysiology of a disease is not clearly related to a particular, usually structural, etiology, it is common to attribute the disease to a psychogenic cause, and this has its roots in the historical tension between holism and dualism.

The concept of holism, from the Greek *holos*, or whole, was first proposed by Plato, Aristotle, and Hippocrates in ancient Greece.<sup>8</sup> Holism postulates that the mind and body are integrated and inseparable, and the study of medical disease must take into account the whole person rather than merely the diseased part. This approach accepts medical symptoms and behavioral disturbances as legitimate features of the individual and traditionally has existed in Eastern cultures.

However, by the 17th century in Western Europe, the concept of holism was eclipsed by the influence of the

philosopher René Descartes, who in 1637 proposed the separation of the thinking mind (*res cogitans*) from the machine-like body (*res extensa*).<sup>2</sup> Descartes's concept of mind–body separation rapidly took hold on the backdrop of evolving sociocultural influences, at the time relating to the separation of church and state. Mind–body dualism had profound effects on how medical disease became conceptualized. Until that time, the body could not be dissected because the spirit was thought to reside there. Medical investigation based on the writings of Galen related to observation of the body and its humors. When the mind–body dualism construct lifted the mind and soul from the realm of the body, human dissection then would be permitted, and this led to emerging knowledge of disease pathology. Over the next few centuries, the morphologic study of disease through pathology, then histopathology, radiology, and nuclear imaging, led to many new diagnoses and treatments for diseases.

However, with a morphologic construct, there was no understanding of symptoms or behaviors in the absence of pathology. In the 17th century, patients showing these features were believed to be under demonic possession and, in later centuries, were considered insane. They were relegated to asylums and were excluded from scientific study. Consequently, another result of Cartesian mind–body dualism is that the study of behavioral abnormalities and mental illness was marginalized; the mind as the seat of the soul was not to be tampered with. Thus, it evolved in Western society that behavioral abnormalities were not available for study, and, in addition, mental illness or physical symptoms in the absence of pathology were considered second class: less legitimate than structural disease and even stigmatized.<sup>9</sup>

In the United States, Benjamin Rush, a prominent physician in the 18th century, sought to integrate psychological and medical knowledge in the diagnosis and treatment of medical illness. However, after his death in 1813, psychiatry was separated from medical practice and mental illness remained unstudied in the asylums. Later in the 1800s, Louis Pasteur's discovery of microorganisms and Robert Koch's development of the germ theory of disease further moved medicine in the direction of biologic reductionism, in which diagnosis was related to specific etiologic agents. However, in recent years (eg, with tuberculosis and acquired immune deficiency syndrome) we now know that infectious agents are conditional factors in disease etiology; host resistance and the social environment also contribute to the clinical expression of the disease.

Because of limited technology, explanatory models of illness and disease through the 19th century developed from natural observations, which then were interpreted in terms of etiology. However, an important advance occurred in 1833 with William Beaumont's studies of Alexis St. Martin, a voyageur who developed a traumatic gastric fistula from a gunshot injury, thus allowing direct observation of gastric mucosal color and secretion. Beaumont's studies systematically reported the association of emotions such as anger and fear with gastric mucosal morphology and function, and was an early psychophysiological investigation of the human GI tract.

### *Early to Mid-20th Century: Observations of Gut and Brain Behavior (1900–1959)*

Beaumont set the stage for further investigations of the effects of emotion on gastrointestinal function. William Cannon noted a cessation in bowel activity among cats reacting to a growling dog. Ivan Pavlov studied surgically produced fistulas in dogs, which led to an understanding of the role of the vagus nerve in mediating the cephalic phase of acid secretion. Later, studies of Tom and Monica, 2 people with gastric fistulas studied by Steward Wolf and George Engel, respectively, showed that different emotional configurations are associated with distinct changes in gastric function.<sup>2</sup> Gastric hyperemia and increased motility and secretion occurred with feelings of anger, intense pleasure, or aggressive behavior patterns related to the subject's active engagement with the environment. Conversely, mucosal pallor and decreased secretion and motor activity occurred with fear or depression: states of withdrawal (giving-up behavior) or disengagement from others. A series of experiments by Tom Almy indicated that physical and psychological stimuli led to increased sigmoid motility and vascular engorgement in healthy subjects and in subjects with irritable colon (irritable bowel syndrome [IBS]).<sup>2</sup> Almy's later studies with healthy subjects and IBS patients using an emotive (stress) interview attempted to correlate mood with motility. In healthy medical students, he noted increased rectal contractility when falsely diagnosed with cancer. He also reported increased motility concurrent with states of aggression (particularly in those individuals with constipation) and decreased motility associated with feelings of helplessness (and diarrhea). Another important observation during this period was by Alvarez,<sup>10</sup> who observed "nongaseous abdominal bloating" in women. He noted that "the pronounced bloating is due not to any excess gas in the digestive tract, but apparently to a contraction of the muscles lining the back and the upper end of the abdominal cavity....In addition there may be a relaxation of the muscles of the anterior abdominal wall."<sup>10</sup> He also reported that the swelling often occurred after a meal. These findings preceded by decades the recent work using more sophisticated assessment methods.<sup>11</sup>

These data provided scientific evidence that the gut is physiologically responsive to emotion and environmental (stressful) stimuli. However, the studies were limited because the measurement techniques were rudimentary, and unidirectional, and did not evaluate the reciprocal effects of changes in gut physiology on mental functioning. Finally, the relation of these observations to actual gastrointestinal symptoms were rudimentary at best.

### *The Biomedical Era: Looking for Disease Specificity: 1960–1979*

With the impressive growth of medical technology after 1960, social and political forces moved scientists into an era of biomedical research. The search for the etiology and pathophysiology of disease took precedence over direct observations of the patient. Psychosocial processes were considered important but only as secondary phenomena,

because "if the cause of a disease could be found and treated, then certainly any psychosocial difficulties would disappear."<sup>9</sup>

**Physiological investigation of the GI tract.** More scientific investigation of gut functioning began in the 1960s with studies of secretory activity using gastrointestinal tubes. By the early 1970s, technological improvements led to new modalities to assess electromechanical function. GI physiologists were developing and testing systems to assess motor and electrical activity of the gut in most areas of the GI tract and were able to delineate mechanisms for many of the esophageal motor disorders (eg, achalasia, scleroderma) and to determine the somewhat paradoxical mechanisms of constipation (increased sigmoid pressures) and diarrhea (decreased pressures).

A logical extension of this research effort was to explore the pathophysiology of the functional GI disorders. These disorders, represented primarily by IBS having both pain and altered gut function, heretofore were unexplained, but the symptoms were presumed to arise from intestinal dysmotility. The studies showed that patients with IBS, when compared with normal subjects, had an enhanced motor response to various environmental stimuli such as psychological stress, peptide hormone and fatty meals, and increased motility was associated, to a degree, with symptoms of pain.

Later in the 1970s, some investigators sought to find biomarkers and one group reported a unique myoelectric pattern, a basic electrical rhythm of 3 cycles/min in patients with IBS, occurring at a frequency up to 40% of the time that was thought to be specific for IBS. However, later work did not reproduce these findings. Investigators also noted that the correlation between altered motility and painful symptoms was poor: experimentally induced motility in IBS did not usually produce pain, and many patients with IBS did not have abnormal motility when having pain.

**Psychosocial and behavioral investigation of functional GI disorders.** For the most part, psychosocial investigation during this period remained out of the mainstream of biomedical research, and was limited to mental health scientists and a few medical investigators whose research was undertaken separately from physiological investigations. Psychological reports showed that patients with IBS had a very high frequency of psychological distress or disturbance. Some investigators then argued that IBS was a psychiatric disorder akin to somatization. The ongoing argument as to whether IBS was medical or psychiatric later was clarified by epidemiologic and biopsychosocial studies in the 1980s that evaluated gastrointestinal function and symptoms along with psychological state simultaneously. It was found that psychosocial distress enabled symptom severity and illness behaviors, which led to health care seeking. Thus, the prevalence of psychological disturbance was greater in IBS patients rather than in those surveyed who have IBS but are not patients.<sup>12,13</sup>

Given the variety of these somewhat dissimilar observations, it was difficult at the time to identify a unifying concept for IBS. In subsequent years, Christensen<sup>14</sup> even questioned the existence of IBS as a distinct entity. Nevertheless his belief that "heterogeneity of pathological

processes must exist in such a diagnostic category”<sup>15</sup> opened the door to research that later identified meaningful biological subsets of IBS or, alternatively, disorders considered distinctly separate from IBS. It also led investigators to consider alternative conceptualizations for the symptoms of IBS relating to a more integrative multi-component model as discussed later.

**Introduction of the Biopsychosocial Model and Neurogastroenterology: 1980 to the Present**

The 1980s began a period of major changes in the psychosocial understanding of GI disease and illness. In the 1960s and 1970s, it was believed that technologic advances would lead to finding a biological cause (and cure) of FGIDs. However, by the end of this period, clinicians and scientists were confronted with the inefficiencies of this model: (1) diagnostic imaging and physiologic assessment did not fully explain the symptoms of many patients presenting with functional complaints, and, conversely, active disease was not necessarily associated with symptoms; (2) the prominence of psychosocial disturbances and illness behaviors with chronic illness, particularly among those seen at referral centers, was not seen among patients with the same diagnoses in the community, and did not correlate well with the observed physiological disturbance or disease pathology; (3) social and political forces along with newer psychosocial assessment methods such as health-related quality of life led to interests away from disease and toward the patients’ illness experiences; and (4) advances in brain–gut physiology yielded findings that could not fit with a dualistic biomedical concept.

**Biopsychosocial (systems) model.** The pivotal event that brought together a unified understanding of health and disease began in 1977 with the publications by George Engel.<sup>1,16</sup> These articles influenced many investigators and

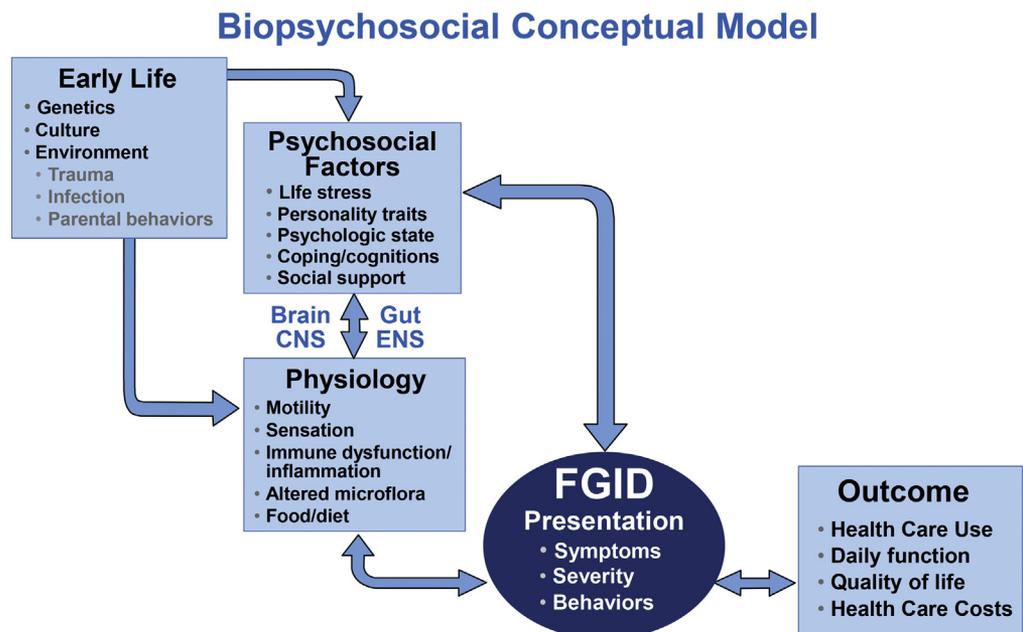
clinicians away from seeking specific underlying biological etiologies to a more integrated, biopsychosocial model of illness and disease.<sup>1,2,16</sup> Engel, an internist and psychoanalyst, offered a modern exposition of holistic (now called *systems*) theory by proposing that illness is the product of biological, psychological, and social subsystems interacting at multiple levels; it is the combination of these interacting subsystems that determines the illness (Figure 1).

The biopsychosocial or systems model offers certain advantages: (1) an understanding of human illness that reconciles the discrepancies between biomedical thought and clinical observation; (2) a clinical framework for the physician to integrate the broad range of biomedical and psychosocial factors that explain the illness experience; and (3) a unifying structure for multidisciplinary research methodology and the inclusion of biopsychosocial assessment in GI illness that emerged over the next few decades. See the article “Biopsychosocial Aspects of FGIDs” for more detail.

The research that evolved led to the following: (1) the development of new questionnaires to assess broader psychosocial domains such as health-related quality of life and coping; (2) a shift in research articles focusing away from solely physiological measurement to those that integrate physiology with patient perceptions and behaviors; (3) inclusion of both psychosocial and physiological assessments in treatment protocols; (4) evaluation of softer outcomes (eg, health care use, daily function, symptom severity, general well-being) than death or disease complications; and (5) use of multivariate statistical methods to simultaneously control for interacting biopsychosocial variables.

**Neurogastroenterology.** By the end of the 1990s, newer clinical and translational techniques relating to gut afferent signaling, neural stimulation and recording, pain perception assessment, evaluation of the association between neural cells and immune functioning, and brain

**Figure 1.** A biopsychosocial conceptualization of the pathogenesis, clinical experience, and effects of functional GI disorders. There is a relationship between early life factors that can influence the psychosocial milieu of the individual, their physiological functioning, as well as their mutual interaction (brain–gut axis). These factors influence the clinical presentation of the disorder and the clinical outcome. Modified from Rome III.<sup>42</sup>



imaging improved our understanding of the interactions between the brain and gut, and this led to the concept of the brain–gut axis. The term *neurogastroenterology* was mentioned in Rome II in 1999 with the basic science and physiology chapters<sup>17,18</sup> as a means to reflect this emerging field of research. In effect, neurogastroenterology reflects the structural and physiological components of the biopsychosocial model, and the latter represents the clinical research and application. The use of neurogastroenterology as a research domain provides a level of legitimacy to gut–brain research as never seen before.<sup>3</sup> Over the past 2 decades, the term has been used by numerous research societies, as well as journals and book publications.

### *Gastrointestinal Symptoms, Syndromes, and Diagnostic Criteria*

The preceding history sets the stage for understanding the place of functional gastrointestinal symptoms and syndromes within gastroenterology, and it provides the basis for the development of diagnostic criteria and the work of the Rome Foundation.

**Concepts of Gastrointestinal Disease, Motility, and Functional GI Disorders.** Table 1 identifies the major clinical domains seen in gastroenterology.

1. The organic (structural) disorders (eg, esophagitis, inflammatory bowel disease) are classified in terms of organ morphology and the criterion for a disease is pathology at a macro- or microlevel.
2. A motility disorder (eg, gastroparesis, intestinal pseudo-obstruction), is classified in terms of organ function and specifically altered motility. Although dysmotility relates to abnormal visceral muscle activity (ie, slow bowel transit, delayed gastric emptying), a motility disorder is presumed to be persistent or recurrent dysmotility recognized as a clinical entity, and variably associated with symptoms. We also recognize that dysmotility may come and go with repeated physiological testing.
3. A functional GI disorder (eg, IBS, functional dyspepsia) relates to the patient's interpretation and reporting of

an illness experience, and it is classified primarily in terms of symptoms. A symptom is a noticeable experiential change in the body or its parts that is reported by the patient as being different from normal and may or may not be interpreted as meaningful. However, a syndrome relates to the association of several clinically recognizable symptoms or signs that occur together to define a clinical entity. A functional GI disorder is a syndrome based on symptoms that cluster together and are diagnosed by Rome criteria.

Notably, there is overlap across these 3 domains. An organic disorder such as ulcerative colitis, identified by gut pathology, may be associated with a motility disturbance and usually is associated with symptoms of pain and diarrhea, but neither the motility disturbance nor the symptoms are necessary for the diagnosis. A motility disorder such as gastroparesis is identified by a persistent motility disturbance (eg, delayed gastric emptying). It may occur from altered gut neuronal morphology and often has symptoms of nausea and vomiting, but patients do not necessarily have symptoms that correlate with the disturbed motility.<sup>19</sup> However, it is the motility finding that characterizes the disorder. Similarly, a functional GI disorder such as IBS or functional dyspepsia may have pathologic findings of inflammatory cells in the lamina propria of the gut or eosinophils in the duodenum, respectively, as well as disturbed motility, but histopathology is not necessary for defining a functional GI disorder. The caveat is that although FGID criteria primarily are symptom-based, there are exceptions, such as with the anorectal disorders, in which physiological findings are part of the criteria. Furthermore, identification of biological substrates may help in terms of subclassification and treatment.

### *History of Rome Criteria for Diagnosis of FGIDs and of the Rome Foundation*

**Pre-Rome: working team publications leading to classification of FGIDs.** This history began in Rome 30 years ago when Aldo Torsoli, Professor of Gastroenterology at the University of Rome, was engaged in developing Working Teams for the International Gastroenterology meetings (held

**Table 1.** Major Clinical Domains in Gastroenterology

	Organic GI disorder	Motility disorder	Functional GI disorder
Primary domain	Organ morphology	Organ function	Illness experience
Criterion	Pathology (disease)	Altered motility	Symptoms
Measurement	Histology Pathology Endoscopy Radiology	Motility Visceral sensitivity	Motility Visceral sensitivity Symptom criteria (Rome) Psychosocial
Examples	Esophagitis Peptic ulcer IBD Colon cancer	Diffuse esophageal spasm Gastroparesis Pseudo-obstruction Colonic inertia	Esophageal chest pain Functional dyspepsia IBS Functional constipation

IBD, inflammatory bowel disease.

in Rome in 1988). By using the Delphi approach, he selected experts from around the world to work through consensus to answer difficult clinical questions that could not be answered through scientific evidence at the time, and present their results at this meeting.<sup>20,21</sup> Torsoli collaborated with W. Grant Thompson, MD, from Ottawa, a respected gastroenterologist studying in the nascent field of FGIDs to form a working team to develop consensus criteria for the diagnosis of IBS. Thompson et al<sup>22</sup> were some of the few experts working on epidemiologic, clinical, and psychosocial investigation of IBS at the time. They then published the first diagnostic criteria for IBS based on consensus.<sup>22</sup>

This IBS working team was generative of the later Rome process, by generating diagnostic criteria by consensus among experts globally. However, IBS was not the only FGID. By the 1980s publications on other nonstructural, symptom-based disorders were being studied: noncardiac functional chest pain<sup>23</sup>; nonulcer dyspepsia<sup>24</sup>; postcholecystectomy pain<sup>25</sup>; bowel disorders related to bloating, diarrhea, and constipation; and anorectal disorders including fecal incontinence, difficult defecation, and rectal pain.<sup>26,27</sup> However, there was no overarching operational definition or classification for them.

In 1989, Torsoli and Corazziari, a collaborator from the University of Rome GI group, approached me to continue the working team process. I proposed that we develop a classification system for all the FGIDs and that we create diagnostic criteria for them. With the support of the journal *Gastroenterology International* we began the process of creating a classification system with diagnostic criteria for all of the FGIDs.

The first committee consisted of experts in the various anatomic regions under consideration. They established 5 anatomic regions (esophagus, gastroduodenal, bowel, biliary, and anorectal), and within each region identified several disorders and for each categorized their clinical features, diagnosis (using symptom-based criteria), and treatment. They worked by e-mail over 2 years and met once in the *Gastroenterology International* office in Rome to consolidate the work and subsequently published it.<sup>28</sup>

**Rome I: 1994.** Over the next few years a series of publications relating to each anatomic domain was elaborated upon and published in *Gastroenterology International*. Each member of the original committee created his own working team of experts and elaborated on the epidemiology, pathophysiology, psychosocial features, diagnostic criteria, and treatment aspects of the diagnoses.<sup>29-33</sup> Also, given the poor standardization of clinical trials in the functional GI disorders,<sup>34</sup> we also created a working team to provide guidelines for proper trials.<sup>35</sup> Finally, with new criteria for 21 functional GI disorders, we created a questionnaire to use in epidemiologic surveys and clinical studies. This questionnaire was applied in the US Householder study, the first national epidemiologic database on the prevalence, demographic factors, and health care-seeking features of people with FGIDs.<sup>36</sup>

In 1994, the articles were compiled into a book: "The Functional Gastrointestinal Disorders: Diagnosis, Pathophysiology, and Treatment"<sup>37</sup> and in retrospect is

considered Rome I. Although the book sales were quite limited, with fewer than 1000 copies sold, the 5 editors and the 32 other internationally recognized committee members creating these chapters began publishing studies using these criteria. From this initiative, the concept of the FGID classification system and diagnostic criteria began to grow in use.

**Rome II: 1999-2000.** By the mid-1990s, 2 factors helped to promote the FGID classification and use of diagnostic criteria: the US Food and Drug Administration recommended the IBS criteria be used to select patients for pharmaceutical studies, and the pharmaceutical industry took interest in supporting the efforts of the Rome Foundation. The Rome Foundation was incorporated in 1996, and with the support of 8 pharmaceutical sponsors an industry council was created as a forum for the exchange of ideas between the Rome Foundation and the sponsors. However, to avoid any perception of influence, this council was separate from the work of the Rome Board of Directors or committees. Then, by the late 1990s, as a result of the increased growth of publications in FGIDs, the Foundation recruited 52 authors representing 13 countries to update the literature and produce the Rome II book by 2000.<sup>38</sup> In addition, to gain Medline access, the committees produced condensed versions of the chapters that were published in a special issue of *Gut* in 1999.<sup>39</sup>

**Rome III: 2006.** After publication of Rome II, the number of studies published using the Rome criteria in clinical trials grew 8-fold over the next 12-14 years. The Industry Advisory Council also expanded to include 12 pharmaceutical companies and at various times representatives from the Food and Drug Administration, Japanese Regulatory Authority, the European Medicines Agency, and the International Foundation of Functional GI Disorders. By 2002, the process began to produce Rome III, with the addition of several new chapters and the recruitment of 87 authors representing 18 countries. Rome III differed from Rome I and Rome II by the use of more evidence-based rather than consensus-based data because research studies were being published using the Rome criteria, which allowed for more precise patient selection and with data more representative of these disorders. The book was published in May 2006,<sup>40</sup> just after the publication of a special Rome III issue of *Gastroenterology*, which contained condensed versions of the book chapters.<sup>41</sup>

**Rome IV: 2016.** After 2006, the Rome Foundation became increasingly recognized as an authoritative body developing diagnostic criteria for research and also for providing education about the FGIDs to clinicians, trainees, and investigators worldwide. However, to meet their goal to advance the field of FGIDs, the Foundation had to address the following limitations: (1) the term *functional GI disorders*, although entrenched in the literature, was imprecise and to some degree stigmatizing; (2) the diagnostic criteria were cumbersome to use in clinical practice; (3) the criteria did not specify the investigative pathway to use before applying the criteria; (4) the criteria oversimplified the full dimension of the patients' illness experience and were not precise enough to identify meaningful physiological

subgroups or biomarkers that might lead to more targeted treatment; and (5) the Foundation traditionally approached knowledge acquisition from a Western base of knowledge, and this was a limitation to other countries and cultures. Thus, the Rome Foundation made efforts to address these limitations with Rome IV, as discussed later and further delineated in the articles that follow. Although perhaps not all of these limitations are addressed fully, Rome IV provides a foundation for future changes that will be made in our understanding of these disorders.

## Definition

The definition of FGIDs has varied based on societal perspectives of illness and disease over time, on the scientific evidence, and on the clinician's training and personal biases. Even today, FGIDs are considered by many as less legitimate than pathologically based diagnoses, and patients with FGIDs may be stigmatized for having symptoms that they consider to be very real. This originated as discussed earlier from the influence of dualistic principles that separate organic disorders, which are attributed by some to be legitimate, and functional disorders, which often are considered psychiatric or undefined.<sup>9</sup> However, over time and with each book publication, the definition has changed from the absence of organic disease to a stress-related or psychiatric disorder to a motility disorder, and with Rome III, to a disorder of GI functioning.<sup>42</sup>

However, there is still a need for a meaningful working definition to approach these disorders scientifically and without bias. To achieve that for Rome IV, the Foundation again relied on the Delphi method<sup>20,21</sup> to create a definition for FGIDs that is positive (rather than by the exclusion of other disease), reflective of current scientific knowledge, and nonstigmatizing. The new definition created by the Board of Directors was shared among the chairs and co-chairs of the Rome IV committees to obtain feedback for modification and, ultimately, approval. The agreed-upon definition is as follows: functional GI disorders are disorders of gut-brain interaction. It is a group of disorders classified by GI symptoms related to any combination of the following: motility disturbance, visceral hypersensitivity, altered mucosal and immune function, altered gut microbiota, and altered central nervous system (CNS) processing.

This definition is most consistent with our evolving understanding of multiple pathophysiological processes that in part or together determine the symptom features that characterize the Rome classification of disorders. We believe it to be readily understood and acceptable to clinicians, academicians, regulatory agencies, and the pharmaceutical industry, as well as to patients.

Although the FGIDs share these physiological features in common, their relative contribution may differ by bodily location, the duration of symptoms, and across individuals or within the same individual over time. For example, fecal incontinence is primarily a disorder of motor function, while centrally mediated abdominal pain syndrome (formerly functional abdominal pain syndrome) primarily is amplified central perception of normal visceral input. However, IBS

appears to be more complex and may result from a combination of factors relating to motility, visceral hypersensitivity, mucosal immune dysregulation, alterations of bacterial flora, and CNS-enteric nervous system dysregulation. In addition, an individual who develops postinfection IBS may have more influence from mucosal immune dysfunction with altered microflora than another individual with the same diagnosis with a lifelong history of chronic symptoms and psychiatric comorbidities relating to altered CNS regulation of GI function. Thus, the classification system is an important component for categorizing these disorders, but effective management requires a biopsychosocial approach that addresses the variability and complexity of patients who have these disorders.

## Rome IV Classification and Criteria for FGIDs

The Rome Foundation classification of FGIDs is based primarily on symptoms rather than physiological criteria.<sup>28</sup> This has been favored because of its utility in clinical care, limited evidence that physiological disturbance (ie, motility) fully explained patient symptoms, and the fact that symptoms are what bring patients to health care providers. However, physiological criteria still are permitted, as for the anorectal disorders, if they increase diagnostic precision. We believe that in the future biomarkers will be included in the criteria if they can enhance their positive predictive value.

The classification of the disorders into anatomic regions (ie, esophageal, gastroduodenal, bowel, biliary, and anorectal) presumes unifying features underlying diagnosis and management that relate to these organ locations. Thus, functional heartburn relates to the esophagus, fecal incontinence to the anorectum, and sphincter of Oddi (SOD) disorder to the biliary system. However, symptom localization is not enough, particularly painful FGIDs (eg, irritable bowel syndrome, functional dyspepsia, and centrally mediated abdominal pain syndrome) are not as easy to localize and are influenced more by overarching effects resulting from CNS-enteric nervous system dysregulation of symptom control pathways.

Table 2 lists the 33 adult and 20 pediatric FGIDs for Rome IV. In this issue, the articles covering the respective anatomic domains listed will discuss the pathophysiology, diagnostic features (including Rome IV criteria), and treatment aspects.

## The Rome Committee Process

In addition to this special issue of *Gastroenterology*, there are other educational materials created to address the limitations stated earlier and that are part of Rome IV: (1) a 2-volume textbook that more comprehensively covers the information provided in this issue; (2) a book on diagnostic clinical algorithms based on common symptom presentations; (3) the Multidimensional Clinical Profile, a case-based method to teach patient care by integrating the multiple (diagnosis, psychosocial, physiological, severity) components contributing to the illness; (4) a book of the

**Table 2.** Functional Gastrointestinal Disorders: Disorders of Gut–Brain Interaction**A. Esophageal Disorders**

A1. Functional chest pain	A4. Globus
A2. Functional heartburn	A5. Functional dysphagia
A3. Reflux hypersensitivity	

**B. Gastroduodenal Disorders**

B1. Functional dyspepsia	B3. Nausea and vomiting disorders
B1a. Postprandial distress syndrome (PDS)	B3a. Chronic nausea vomiting syndrome (CNVS)
B1b. Epigastric pain syndrome (EPS)	B3b. Cyclic vomiting syndrome (CVS)
B2. Belching disorders	B3c. Cannabinoid hyperemesis syndrome (CHS)
B2a. Excessive supragastric belching	B4. Rumination syndrome
B2b. Excessive gastric belching	

**C. Bowel Disorders**

C1. Irritable bowel syndrome (IBS)	C2. Functional constipation
IBS with predominant constipation (IBS-C)	C3. Functional diarrhea
IBS with predominant diarrhea (IBS-D)	C4. Functional abdominal bloating/distension
IBS with mixed bowel habits (IBS-M)	C5. Unspecified functional bowel disorder
IBS unclassified (IBS-U)	C6. Opioid-induced constipation

**D. Centrally Mediated Disorders of Gastrointestinal Pain**

D1. Centrally mediated abdominal pain syndrome (CAPS)
D2. Narcotic bowel syndrome (NBS)/ Opioid-induced GI hyperalgesia

**E. Gallbladder and Sphincter of Oddi (SO) Disorders**

E1. Biliary pain
E1a. Functional gallbladder disorder
E1b. Functional biliary SO disorder
E2. Functional pancreatic SO disorder

**F. Anorectal Disorders**

F1. Fecal incontinence	F2c. Proctalgia fugax
F2. Functional anorectal pain	F3. Functional defecation disorders
F2a. Levator ani syndrome	F3a. Inadequate defecatory propulsion
F2b. Unspecified functional anorectal pain	F3b. Dyssynergic defecation

**G. Childhood Functional GI Disorders: Neonate/Toddler**

G1. Infant regurgitation	G5. Functional diarrhea
G2. Rumination syndrome	G6. Infant dyschezia
G3. Cyclic vomiting syndrome (CVS)	G7. Functional constipation
G4. Infant colic	

**H. Childhood Functional GI Disorders: Child/Adolescent**

H1. Functional nausea and vomiting disorders	H2a1. Postprandial distress syndrome
H1a. Cyclic vomiting syndrome (CVS)	H2a2. Epigastric pain syndrome
H1b. Functional nausea and functional vomiting	H2b. Irritable bowel syndrome (IBS)
H1b1. Functional nausea	H2c. Abdominal migraine
H1b2. Functional vomiting	H2d. Functional abdominal pain – NOS
H1c. Rumination syndrome	H3. Functional defecation disorders
H1d. Aerophagia	H3a. Functional constipation
H2. Functional abdominal pain disorders	H3b. Nonretentive fecal incontinence
H2a. Functional dyspepsia	

Rome IV criteria and validated questionnaires to make a diagnosis in adults and children for research and clinical care; (5) a primary care book; (6) a pediatric book; (7) more than 800 graphic images to be used as slides and in the online book; and (8) translations of the criteria to be used for a global epidemiology survey to understand cross-cultural differences in symptom experience and presentation.

To accomplish this, Rome IV used a rigorous process of prospective and retrospective data gathering, data synthesis, data presentation, group decision making, and extensive peer-review as indicated by the following process.

1. In 2008 the Rome Foundation Board of Directors identified key areas to acquire preliminary knowledge for the Rome IV chapter committees to use. Committees were created to evaluate, compile, and publish reviews in these areas of interest: brain imaging,<sup>43</sup> severity in IBS<sup>44</sup> intestinal microbiota,<sup>45</sup> food/diet and FGIDs,<sup>46-51</sup> cross-cultural research (2014),<sup>52,53</sup> development of an Asian questionnaire to address cross-cultural differences in symptom interpretation,<sup>54</sup> and primary care.<sup>55</sup>
2. Between 2010 and 2012 the Rome IV Editorial Board was created, and they identified the chairs and co-chairs of the 18 committees who in turn selected their committee members to produce the Rome IV chapters
3. Support committees were created to provide ancillary service to the chapter committees: (1) a Questionnaire Committee to develop and validate the Rome IV diagnostic criteria and create research questionnaires, (2) a Systematic Review Committee to perform systematic reviews and meta-analyses for the chapter committees, (3) a Multidimensional Clinical Profile committee to develop a case-based book designed to improve patient care by using a multicomponent assessment to target better treatments,<sup>56</sup> and (4) a Primary Care Committee to assess and publish perspectives of primary care physicians relating to IBS and FGIDs, and to create a primary care book on Rome IV.
4. During Digestive Diseases Week 2013, the chapter committees participated in an orientation in which the support committees presented their work and the new chapter committees were tasked to develop online and printed book manuscripts and a journal article for *Gastroenterology*. They also were requested to develop graphs and images for the online book version, a revision of the Rome III diagnostic algorithms,<sup>57</sup> and a revision with additional cases for the Multidimensional Clinical Profile book.<sup>56</sup>
5. From 2013 through the end of 2015 the committee members critically synthesized the literature and created the requested documents through several revisions.
6. In December 2014 the chapter committees met in Rome (Rome IV Conference 2014) to revise the documents and establish a consensus on the diagnostic criteria and scientific content.
7. At the end of the Rome meeting, the editorial board and the chairs and co-chairs held a full-day harmonization meeting to summarize and present their committees' recommendations to the group. This led to feedback and discussion relating to gaps or redundancies in content that were reconciled by consensus.
8. The documents then were sent to up to 5 outside international experts for peer-review and the documents were modified further as needed.
9. By autumn 2015, the manuscripts for the 13th issue of *Gastroenterology* were created and reviewed by the editorial board of Rome IV.
10. Finally, the committee members signed off on all documents before it was sent to the copy editor for a final check on content and style before publication.

### Limitations in Using Rome Criteria for Diagnosis and Management in Clinical Practice

The Rome symptom-based categoric criteria are of particular value for clinical research and pharmaceutical trials. They provide a clear strategy for selecting study subjects, they are endorsed by regulatory agencies, and are used by clinical investigators and industry for clinical trials around the world. Nevertheless, there are limitations for use in clinical practice. A categoric diagnosis may exclude patients who do not fully meet these criteria but who could be treated similarly. A patient with abdominal pain and bowel dysfunction for fewer than 6 months or fewer than 1 episode a week, or who does not meet 2 of the 3 criteria associating pain with bowel habit, or who has pain not associated with altered bowel habit, would not be diagnosed by criteria as having IBS, yet the clinician could still judge a need for treatment. Furthermore, patients can have 2 or more FGID diagnoses (eg, IBS and functional dyspepsia), although for the purpose of clinical trials the Rome IV criteria exclude this co-occurrence. Thus, for clinical practice, meeting criteria may not be necessary in the daily care of patients but still can serve as a useful guide to help characterize these disorders.

Also, a diagnosis per se does not capture all dimensions of the patient's clinical condition to optimize treatment. For example, a patient meeting criteria for functional dyspepsia may have only occasional symptoms with no lifestyle impairment and not require treatment. In contrast, another patient with the same diagnosis with severe and disabling pain, major depression, and weight loss from eating restrictions needs to be managed quite differently. In addition, the criteria for cyclic vomiting syndrome does not require the presence of pain, yet patients who meet criteria for this diagnosis but who also have pain are more disabled, with

more health care visits, and a greater likelihood of being prescribed opioids leading to other complications. To address these limitations in classification, the Multidimensional Clinical Profile method teaches individualized treatment based on identifying and integrating the multiple components (psychosocial, clinical, physiological, quality of life, and impact aspects) of the symptom experience.<sup>56</sup>

## Changes for Rome IV

Rome IV changes are as follows.

1. The addition of new diagnoses with known etiologies. Narcotic bowel syndrome (opioid-induced gastrointestinal hyperalgesia) has been added to the Centrally Mediated Disorders of Gastrointestinal Pain article, opioid-induced constipation has been added to the Bowel article, and cannabinoid hyperemesis syndrome has been added to the Gastroduodenal article. These diagnoses differ from other FGIDs by having substances (opioids and cannabinoids) that produce the symptoms, and their avoidance may lead to recovery. Because these diagnoses result from known etiologies, they are not truly functional, but we include them in Rome IV because they fit the new definition: disorders of gut–brain interaction being characterized by altered function of the CNS or enteric nervous system; their clinical presentations are similar to FGIDs and thus need to be distinguished from them; and they have not yet been well characterized or reached a level of acceptance in the field to be considered separate disorders (such as lactose intolerance, microscopic colitis).
2. Removal of functional terminology when possible. The debate to retain or change the term *functional* has existed for decades, however, the word “functional” has become so embedded in our health care nosology that it cannot easily be substituted at this time. However, the word “functional” has limitations by being nonspecific and potentially stigmatizing. Therefore, we provide an improved definition of FGIDs (ie, disorders of gut–brain interaction) to help clarify its meaning. In addition, we have removed the word functional from article titles (eg, Esophageal Disorders rather than Functional Esophageal Disorders) and from certain diagnoses (eg, fecal incontinence instead of functional fecal incontinence) as occurred in Rome III. In addition, functional abdominal pain syndrome has been changed to centrally mediated abdominal pain syndrome to more appropriately address the disorder’s pathogenesis, minimize the stigma of the term *functional*, and reverberate with the new brain–gut information that is emerging. However, some clinical disorders (eg, functional diarrhea, functional heartburn) have retained the term to distinguish them from disorders having similar symptoms but with clear structural etiologies.
3. Article additions and modifications. A new article entitled Intestinal Microenvironment and the Functional Gastrointestinal Disorders combines knowledge of the microbiome, food, and nutrition to improve understanding of the luminal aspects of GI function. Pharmacological and Pharmacokinetic Aspects of Functional GI Disorders has been changed to Pharmacological, Pharmacokinetic, and Pharmacogenomic Aspects of Functional Gastrointestinal Disorders to include the role of genetics in the clinical response to pharmaceutical treatments. Gender, Age, Society, Culture and the Patient’s Perspective from Rome III has been split into 2 articles to reflect the rapid growth of knowledge in these areas of Age, Gender, Women’s Health, and the Patient and Multicultural Aspects of Functional Gastrointestinal Disorders. Psychosocial Aspects of Functional Gastrointestinal Disorders has been changed to Biopsychosocial Aspects of Functional Gastrointestinal Disorders to reflect the multidetermined nature of biopsychosocial processes. The Rome III article Functional Abdominal Pain Syndrome is changed to Centrally Mediated Disorders of Gastrointestinal Pain to reflect the predominant CNS contribution to the symptoms.
4. Threshold changes for diagnostic criteria. With limited information on normal bowel symptom frequencies and inadequate data from the literature on the frequency of GI symptoms using Rome criteria, the Foundation conducted a Normative Symptom Study so the chapter committees can include evidence-based thresholds for judging symptoms as out of the range of normal. The Rome Foundation Questionnaire Committee conducted a survey of physical symptoms including FGID symptoms on a nonclinical nationwide sample in the United States. Using this information, frequency thresholds were created for the diagnostic criteria that were different from general sample frequencies.
5. Addition of reflux hypersensitivity diagnosis. In Rome III, Functional Heartburn defined heartburn symptoms in the absence of evidence that the heartburn is associated with gastroesophageal reflux. However, there also are patients who have normal acid reflux levels, but they are sensitive to the physiological reflux and so develop heartburn. For Rome IV, A3 Reflux Hypersensitivity characterizes this situation and is to be differentiated from A2 Functional Heartburn or even nonerosive reflux disease by their greater association of symptoms with reflux, albeit physiological.
6. Revision of SOD disorder criteria. Recommendations<sup>58</sup> to perform biliary sphincterotomy based on clinical criteria (biliary dilatation and increased liver chemistries or increased pancreatic enzyme levels) for presumed sphincter of Oddi pain has not had

convincing supportive evidence. Thus, balancing the benefits of symptomatic relief with the potential risks of pancreatitis, bleeding, and perforation has been challenging, and the Rome III criteria for these disorders were not particularly helpful in providing proper guidelines. Now, driven by evidence that debunks the value of sphincterotomy for type III SOD,<sup>59</sup> the Gallbladder and Sphincter of Oddi Disorders chapter committee has reclassified these disorders, and they provide a more rational algorithm for treatment. The previous type III SOD categorization of the Milwaukee classification has been removed, so patients without evidence of bile duct obstruction should not be referred for endoscopic retrograde cholangiopancreatography with manometry for possible sphincterotomy. Instead, they should be treated symptomatically. In addition, treatment of functional biliary sphincter of Oddi disorder in patients with only moderate objective evidence of biliary obstruction should consider other investigative options before a decision for sphincterotomy is entertained.

7. Functional bowel disorders now exist on a spectrum of symptom presentations. The predominant bowel diagnoses of IBS with subtypes of constipation, diarrhea, mixed, and unclassified, are no longer considered distinct disorders. Instead, they exist on a spectrum with linked pathophysiological features that are variably expressed clinically by patient-specific differences in the quantity, intensity, and severity of symptoms. This overlap of clinical features is well observed for IBS with predominant constipation and chronic constipation in which categories may switch depending on the degree of pain and across the subcategories of IBS related to changes in stool habit over time.<sup>60-63</sup> This also can occur for IBS with functional dyspepsia or functional constipation with pelvic floor dyssynergia. For clinical trials, specific diagnostic criteria are necessary to assess the targeted effects of the drugs, however, in clinical care, patients may transition from one diagnosis to another or have combinations of diagnoses that may require overarching management (eg, antidepressants for pain across multiple diagnoses).
8. Change in identification of IBS subtypes. The Rome III classification for IBS subtypes required that the proportion of total stools using the Bristol Stool Form Scale be used to classify IBS with predominant diarrhea (>25% loose/watery, <25% hard/lumpy), IBS with predominant constipation (>25% hard/lumpy, <25% loose/watery), mixed-type IBS (>25% loose/watery, >25% hard/lumpy), and IBS unclassified (<25% loose/watery, <25% hard/lumpy). However, because patients can have large periods of time with normal stool consistency, there is a large number of patients with unclassified IBS subtype relative to the other groups.<sup>64,65</sup> Based on

this observation and the results of a Rome Foundation Normative Symptom Study, the criteria for subtypes of IBS have been changed and relate to the proportion of symptomatic stools (ie, loose/watery and hard/lumpy) rather than all stools (including normal ones). As a result, the unclassified group is reduced markedly.

9. Removal of the term *discomfort* from IBS criteria. The Rome III criteria for IBS required abdominal pain or discomfort, presuming that these terms exist on a continuum from more severe (pain) to less severe (discomfort). However, more recent data<sup>66</sup> have indicated that patients consider the two terms as qualitatively different, and discomfort can incorporate a variety of symptoms. In addition, the term *discomfort* has different meanings and is reported with different frequencies across cultures.<sup>67</sup> Therefore, to avoid symptom-related and cultural heterogeneity, only the term *pain* is used as the key diagnostic criterion for IBS.
10. Combined nausea and vomiting disorder. For Rome IV the new diagnosis B3a. Chronic Nausea Vomiting Syndrome combines the previous Rome III entities Chronic Idiopathic Nausea and Functional Vomiting. This is owing to a lack of evidence delineating different diagnostic approaches and management of nausea compared with vomiting, and the clinical observation that these 2 symptoms commonly are associated. Although we recognize that patients may present only with nausea, the clinical approach to diagnosis and management is still the same.

### Biopsychosocial Model of Functional GI Disorders

Figure 1 shows an updated Biopsychosocial Conceptual Model for functional gastrointestinal disorders<sup>68</sup> (see the article Biopsychosocial Aspects of Functional Gastrointestinal Disorders). Early in life, genetics, sociocultural influences, and environmental factors may affect one's psychosocial development in terms of personality traits, susceptibility to life stresses, psychological state, and cognitive and coping skills. These factors also influence the susceptibility to gut dysfunction: abnormal motility or sensitivity, altered mucosal immune dysfunction or inflammation, and the microbial environment, as well as the effect of food and nutritional substances. Furthermore, these brain-gut variables reciprocally influence CNS expression.

An FGID is the product of these interactions of psychosocial factors and altered gut physiology via the brain-gut axis.<sup>68,69</sup> Thus, an individual with bacterial gastroenteritis who has a reduced inoculation of bacteria, no concurrent psychosocial difficulties, and good coping skills may not develop a clinical syndrome and, if it does develop, may have mild symptoms and not perceive the need to seek medical care. Another individual with a larger inoculation of

bacteria or a longer period of gastroenteritis, co-existent psychosocial comorbidities, high life stress, abuse history, or maladaptive coping may develop a severe syndrome of postinfection IBS or dyspepsia, go to the physician frequently, and have a generally poorer outcome.<sup>70–73</sup> Furthermore, the clinical outcome will, in turn, affect the severity of the disorder (Figure 1, double-sided arrow). For example, a family that addresses the illness behavior adaptively and attends to the individual and his or her psychosocial concerns may reduce the impact of the illness experience and resultant behaviors. Conversely, a family that is overly solicitous to the person's illness<sup>74</sup> or a societal group that interprets certain symptoms with threat may amplify the symptoms and illness behaviors. With regard to management, when the physician acknowledges the reality of the patient's complaints, provides empathy, and engages in an effective physician–patient interaction, symptom severity and health care seeking are reduced.<sup>75</sup> In contrast, the physician who does not engage in these skills and who repeatedly performs unnecessary diagnostic studies to rule out pathologic disease, dismisses the patient's concerns, or does not collaborate effectively in the patient's care, is likely to promote a vicious cycle of symptom anxiety and health care seeking.<sup>76</sup>

### Biopsychosocial Overview of Functional GI Disorders

Using Figure 1 as a template, the concepts and associations of this model are discussed briefly and covered in more detail in the article Biopsychosocial Aspects of Functional Gastrointestinal Disorders.

**Early life.** A person's genetic composition and interactions with the environment affect later susceptibility to disease, their phenotypic expression, as well as patient attitudes and behaviors (including health care seeking) relating to it. Family and twin studies have indicated a genetic component to IBS and likely other FGIDs, with several polymorphisms and candidate genes that can affect physiological functioning including motor function, membrane permeability, and visceral sensitivity.<sup>77</sup> However, Mendelian single-gene susceptibility is unlikely; rather, multiple genes likely interact with environmental risk factors to produce the clinical heterogeneity among individuals with FGIDs,<sup>78</sup> and psychophysiological factors such as stress may affect the epigenetic expression of these genes, leading to visceral hypersensitivity and other functions associated with these disorders.<sup>79</sup>

Sociocultural factors and family interactions shape later reporting of symptoms, the development of FGIDs, and health care seeking. The expression of pain varies across cultures from denial to stoicism to dramatic expression. Symptoms such as bloating are reported commonly in China, however, there is no word for bloating in Latin cultures. With regard to health care use, diarrhea is highly prevalent in Mexico and may not be considered an illness leading to health care visits,<sup>5</sup> and, in general, rural Latin Americans are more likely to go to a local health care provider, a *curandero*, for common illnesses, and reserve seeing

a traditional medical provider for more serious or life-threatening diseases.<sup>4</sup>

Environmental exposures such as childhood *Salmonella* infection can be a risk factor for IBS in adulthood.<sup>70</sup> Early learning difficulties or emotionally challenging interactions in childhood may predispose to FGIDs. For example, difficulties surrounding bowel habit<sup>80</sup> or early abuse<sup>81</sup> may result in encopresis and even painful dyssynergic defecation later in life, which can be reconditioned through anorectal biofeedback.<sup>82</sup> Early family attention toward GI symptoms and other illnesses can influence later symptom reporting, health behaviors, and health care costs.<sup>74</sup>

**Psychosocial factors.** Although psychosocial factors are not required for diagnosis, they influence physiological functioning of the GI tract via the brain–gut axis (motility, sensitivity, barrier function), are modulators of the patient's pain experience and symptom behavior, and, ultimately, affect treatment selection and the clinical outcome (see article Biopsychosocial Aspects of FGIDs). When evaluating for psychosocial factors, the clinician should consider four general observations:

1. Psychological stress or one's emotional response to stress exacerbates gastrointestinal symptoms and may contribute to FGID development. This occurs among healthy subjects and patients with structural diagnoses, and is well demonstrated in patients who develop functional gastrointestinal disorders, a common example being postinfection IBS or dyspepsia.<sup>71</sup> We also see a high association of psychosocial comorbidities, life stress, and abuse among patients with FGIDs, which lead to poorer outcomes.
2. Psychosocial factors modify the experience of illness and illness behaviors such as health care seeking. Although patients with FGIDs show greater psychological disturbance than otherwise healthy subjects and patients with medical disease, the data are drawn from patients seen at referral centers. This explains why psychosocial trauma (eg, sexual or physical abuse history) is more common in referral centers than in primary care, may decrease the pain threshold and symptom reporting, and is associated with a poorer clinical outcome.<sup>72</sup> These factors can be reduced or buffered by adaptive coping skills and social support. Thus, it follows that the psychosocial response of family, society, and culture also can have a palliative effect on the illness experience.
3. A functional GI disorder may have psychosocial consequences. Any chronic illness has psychosocial consequences on one's general well-being, daily function status, and sense of control over the symptoms, as well as implications of the illness in terms of future functioning at work and at home. This is understood in terms of one's health-related quality of life.
4. Psychosocial effects of illness, namely emotional distress and maladaptive cognitions, may feed back to perpetuate and amplify symptoms. Patients with

severe symptoms may develop a morbid pessimism and helplessness (ie, catastrophize) and selectively attend to and be hypervigilant to their symptoms, leading to visceral anxiety, all of which decreases sensation thresholds and produces feelings of poor self-efficacy and self-esteem. In these cases, a behavioral intervention is needed to help re-establish a psychological substrate of improved health.

**Physiology.** A variety of physiological processes may lead to GI symptoms and, when more prevalent, to functional GI disorders.

**Abnormal motility.** Disturbed gastrointestinal motility can generate symptoms of nausea, vomiting, diarrhea, acute abdominal pain, incontinence, and others. Furthermore, in healthy subjects, and more so in patients with FGIDs, strong emotion or environmental stress via the brain-gut axis can lead to dysmotility throughout the GI tract. FGIDs have an even greater motility response to stressors when compared with normal subjects.<sup>83</sup> However, these motor responses only partially are correlated with symptoms, and are not sufficient to explain reports of chronic or recurrent abdominal pain.

**Visceral hypersensitivity.** The poor association of pain with GI motility with many functional GI disorders (eg, functional chest pain, functional dyspepsia-epigastric pain syndrome, IBS, and so forth) is explained by the concept of visceral hypersensitivity.<sup>84</sup> These patients have a lower pain threshold with balloon distension of the bowel (visceral hyperalgesia), or they have increased sensitivity even to normal intestinal function (eg, allodynia). Visceral hypersensitivity may be amplified in patients with FGIDs: repetitive balloon inflations in the colon lead to a progressive although transient increase in pain intensity in healthy subjects and for a longer period in patients with FGIDs. Hypersensitivity and sensitization may be amplified at all levels of the brain-gut axis such as by factors listed later.

**Immune dysregulation, inflammation, and barrier dysfunction.** The work on postinfection IBS and dyspepsia have been associated with increased interest in mucosal membrane permeability via alteration of tight junctions,<sup>85</sup> the intestinal flora, and altered mucosal immune function.<sup>86</sup> These associations increase the access of intraluminal antigens into the submucosa associated with low-grade activation of mast cells and increased inflammatory cytokine release.<sup>87</sup> These actions alter receptor sensitivity at the gut mucosa and myenteric plexus, producing visceral hypersensitivity. Factors contributing to this occurrence include genetics, psychological stress via mast cell activation, and altered receptor sensitivity at the gut mucosa and myenteric plexus. This is enhanced by alteration of the bacterial environment or outright infection.

**Microbiome.** The microbiome represents the collection of microorganisms, which is shaped by host factors such as genetics and nutrients, but in turn is able to influence host biology in health and disease. It has become a major area for research in gut functioning in the FGIDs, and there is also an emerging concept of the microbiome-gut-brain axis.<sup>69,88</sup>

Differences among IBS patients in the bacterial composition of the gut (eg, increased *firmicutes* and reduced *bacteroidetes* and *bifidobacter*), and also reduced fecal microbial diversity relative to healthy individuals, have implied a causative role in the onset and maintenance of IBS. This is supported by the modest effect of probiotics and more substantive benefit of periodic antibiotic treatment in improving IBS symptoms.<sup>45</sup> However, further research is needed to fully understand the place of the bacterial flora in the pathogenesis of FGIDs.

**Food, diet, and intraluminal factors.** A recent addition to understanding FGIDs relates to food and diet<sup>46</sup> and also their relationship to intestinal microbiota.<sup>89</sup> Certain specific alterations in diet such as low fermentable oligo-, di-, and monosaccharides and polyols, or gluten restriction in some patients, may provide benefit as a result of reduced osmotic effects or alterations in gut mucosa. However, no one diet is of specific value and treatment must be individualized. In addition, the diet provides substrates for microbial fermentation, and because the composition of the intestinal microbiota is altered in IBS, the link between food and diet, microbiota composition, and fermentation products may play an important role in IBS pathogenesis. This is noteworthy because there has been a discrepancy between patients' and physicians' attributions to the effect of food on FGID symptoms, with patients believing the effect was more relevant.<sup>90</sup> Further study is needed to define the subsets of patients who are more likely to respond to alterations in diet.

Another recent area of interest relates to the effect of intraluminal factors in addition to maldigested nutrients on gut function. This includes microflora alterations in short-chain fatty acids; the products of enteroendocrine cells including granins and their effect on nervous, endocrine, and immune cells; and the proportion of secondary to primary bile acids, possibly affecting gut-transit rates.<sup>83</sup> For example, the prevalence and role of choleraic enteropathy likely has been underestimated previously in conditions such as diarrhea-predominant IBS, and when recognized can lead to a more specific treatment using bile acid binders.

**Brain-gut axis.** The brain-gut axis is the neuroanatomic substrate in which the psychosocial factors just described influence the GI tract and vice versa. The hardwiring between the brain and gut is a complex integrated circuitry that communicates information from emotional and cognitive centers (subserving thoughts, feelings, memories, and pain regulation) of the brain via neurotransmitters (software) to the peripheral functioning of the GI tract and vice versa.<sup>91</sup> Structurally, there are direct connections between the CNS and myenteric plexus to the visceral muscles and other end-organ structures that affect sensory, motor, endocrine, autonomic, immune, and inflammatory function.<sup>92</sup> Thus, emotions such as fear, anger, anxiety, painful stimuli, and physical stress can delay gastric emptying and intestinal transit. They also can stimulate colonic motor function, reflected by decreased colonic transit time, increased contractile activity, the induction of defecation, and symptoms of diarrhea. Also, psychological

stress can disrupt the gut-pain threshold and impair mucosal secretory and barrier functions, and this is associated with transmigration of bacterial cell products leading to GI pain and diarrhea, as with IBS. Conversely, enhanced motility, visceral inflammation, and injury can amplify ascending visceral pathways and affect brain areas, leading to greater pain and contributing to altered mental functioning including anxiety and depression. In effect, the reciprocal relationships that we call the brain-gut axis is the neuroanatomic and neurophysiologic substrate for the clinical application of the systems or biopsychosocial model.<sup>93</sup>

With regard to pain regulation, the relationships between psychosocial distress and painful symptoms appears mediated through impairment in the ability of various brain networks such as the cingulate cortex to process bodily pain. In effect, the brain's pain control system can act as a filter to enhance or block pain by up-regulating or down-regulating the incoming neural signals affecting symptom perception through this gate control mechanism. Down-regulation, which increases the pain threshold, seems not to occur as well in patients with functional GI pain. The anterior cingulate cortex, involved in the motivational and affective components of the emotional arousal and salience network, is dysfunctional with IBS and other functional GI pain, fibromyalgia, and other functional somatic symptoms. When this system is influenced by psychosocial distress, the gate is open and the pain threshold is decreased. Conversely, improvement in pain control can be enabled by cognitive or emotional factors such as focused attention, hypnosis, psychological treatment, and certain antidepressants. These effects may be more than physiological based on growing evidence for their role in enhancing neurogenesis as well, thus possibly contributing to more lasting effects for these treatments.<sup>94</sup> A more recent understanding expands upon the complexity of multiple brain network operating systems including emotional arousal, salience and executive functions, sensorimotor and autonomic functions related to FGIDs.<sup>93</sup> In sum, the clinical phenotype that we understand as FGIDs emerges from the interactions of multiple systems in the periphery (microbiome, altered mucosal inflammation, visceral hypersensitivity) and in the brain (brain network systems of emotional arousal, sensorimotor function, central autonomic function) interacting with each other in bidirectional ways that lead to the FGID phenotype.<sup>93</sup>

**FGID symptom experience severity and behavior.** The product of the interacting effects of the brain and GI tract in any individual with an FGID relates to the clinical expression of illness; namely, the symptom experience, its severity, and subsequent illness-related behaviors. This includes the meaning of illness, the fears of continued symptoms, the perceived concerns relating to alterations in body image, social acceptability (eg, feeling stigmatized), the degree of functional impairment with its implications at work and at home, the sense of helplessness to effect symptom relief, and the difficulty of coping with disability must all be dealt with by the patient. How well the patient adapts based

on personal and family resources, in addition to the quality of the physician's involvement, is crucial to the patient's psychological well-being and clinical course. Given the proper biopsychosocial milieu, many patients can adapt to their illness with some support from family, friends, and health care providers. Other patients, possibly shaped by genetics and early experiences, respond by feeling helpless and unable to feel in control of their symptoms and the effects on their life; they regress and become dependent. Their continued symptoms, restricted activity, and health care needs may tax family, friends, and their physician, all of whom may feel helpless to provide enough emotional or medical assistance. If the patient has a limited capacity to cope psychologically with the illness, the disorder is particularly incapacitating, or if the interpersonal family relationships are dysfunctional, additional efforts by the physician and ancillary personnel (eg, psychological counselors, social workers, peer support groups) will be required.

**Outcome.** The outcome of the biopsychosocial model as discussed is what we see in the patient's health and personal care behaviors, and in the impact on family, the physician, and society. Psychosocial factors are strong determinants of medication use, health care visits, functional ability, loss of work time, and health care costs. All of these factors can be addressed and potentially modified by the physician's ability to listen, engage, and effect good communication skills, as discussed later, regardless of the diagnostic condition.<sup>75</sup>

## An Approach to the Care of Patients With Functional GI Disorders

### *Twelve Steps to Enhance the Therapeutic Relationship*

An effective physician-patient relationship can improve patient satisfaction, adherence to treatment, symptom reduction, and other health outcomes. This section provides general care guidelines that can help to optimize this relationship for patients with FGIDs.<sup>75</sup>

1. Improve patient satisfaction and engage with the patient. Patient satisfaction relates to the patient's perception of the doctor's humaneness, technical competence, interest in psychosocial factors, and provision of relevant medical information, and too much focus on biomedical issues can have a negative effect. Engagement relies on nonverbal communication: good eye contact, affirmative nods, gentle tone of voice, close interpersonal distance, and creation of a partner-like interaction.
2. Obtain the history through a nondirective, nonjudgmental, patient-centered interview. This involves active listening and using questions based on the patient's thoughts, feelings, and experiences rather than on using a personal or preset agenda of questions.

**Table 3.** Proposed Clinical Profile for Patient-Rated Severity in IBS<sup>44</sup>

Clinical feature estimated prevalence	Mild 40%	Moderate 35%	Severe 25%
Psychometric correlate	FBDSI, <36 IBS-SSS, 75–175	FBDSI, 36–109 IBS-SSS, 175–300	FBDSI, >110 IBS-SSS, >300
Physiological factors	Primarily bowel dysfunction	Bowel dysfunction and CNS pain dysregulation	Primarily CNS pain dysregulation
Psychosocial difficulties	None or mild psychosocial distress	Moderate psychosocial distress	Severe–high psychosocial distress, catastrophizing, abuse history
Sex	Men = women	Women > men	Women >>> men
Age	Older > younger	Older = younger	Younger > older
Abdominal pain	Mild/intermittent	Moderate, frequent	Severe/very frequent or constant
Number of other symptoms	Low (1–3)	Medium (4–6)	High (≥7)
Health-related quality of life	Good	Fair	Poor
Health care use	0–1/y	2–4/y	≥5/y
Activity restriction	Occasional (0–15 days)	More often (15–50 days)	Frequent/constant (>50 days)
Work disability	<5%	6%–10%	≥11%

NOTE. Based on Drossman et al.<sup>44</sup>

FBDSI, Functional Bowel Disorder Severity Index; IBS-SSI, IBS Symptom Severity Index.

- Determine the immediate reason for the patient's visit (eg, What led you to see me at this time?) and evaluate the patient's verbal and nonverbal communication. Some possible reasons include the following: (a) new or exacerbating factors (dietary change, concurrent medical disorder, side effects of new medication), (b) personal concern about a serious disease (eg, recent family death), (c) personal or family stressors (eg, recent or anniversary of death or other major loss, abuse event, or history), (d) worsening or development of psychiatric comorbidity (depression, anxiety), (e) impairment in daily function (recent inability to work or socialize), or (f) a hidden agenda such as narcotic or laxative abuse or pending litigation or disability claims.
- Conduct a careful physical examination and cost-efficient investigation. A well-conducted physical examination has therapeutic value.<sup>95</sup>
- Determine what the patient understands of the illness and his or her concerns (eg, What do you think is causing your symptoms? or What concerns or worries do you have about your condition?).
- Elicit the patient's understanding of the symptoms (illness schema) and provide a thorough explanation of the disorder that takes into consideration the patient's beliefs. For example: "I understand you believe you have an infection that has been missed; as we understand it, the infection is gone but your nerves have been affected by the infection to make you feel like it is still there, similar to a phantom limb."
- Identify and respond realistically to the patient's expectations for improvement (eg, How do you feel I can be helpful to you?).
- When possible, provide a link between stressors and symptoms that are consistent with the patient's beliefs. Many patients are unable or unwilling to associate stressors with illness but most patients will understand the stress of the illness on their emotional state: "I understand you do not see stress as causing your pain, but you have mentioned how severe and disabling your pain is. How much do you think that is causing you emotional distress?"
- Set consistent limits (eg, I appreciate how bad the pain must be, but narcotic medication is not indicated because it can be harmful).
- Involve the patient in the treatment (eg, Let me suggest some treatments for you to consider).
- Make recommendations consistent with patient interests (eg, Antidepressants can be used for depression, but they also are used to "turn down" the pain, and pain benefit occurs in doses lower than that used for depression).
- Help establish an ongoing relationship with you or in association with a primary care provider (eg, Whatever the result of this treatment, I am prepared to consider other options, and I will continue to work with you through this).

### Symptom Severity as a Guide to Treatment

Although illness severity exists on a continuum, there is heuristic value in separating FGIDs into mild, moderate, and severe categories in planning treatment. Table 3 applies primarily to IBS patients, the group that has been most studied. Although this information may not fully represent non-health care seekers or patients with other FGIDs, it is presented to help the clinician understand the variability in symptom reports, illness behaviors, and treatment recommendations all based on severity factors. In general, the greater the severity the more intervening psychosocial and

other comorbidities will influence the clinical presentation and will require different treatments.

**Mild symptoms.** Patients with mild or infrequent symptoms comprise approximately 40% of patients, are seen more in primary care than in gastroenterology practices, and do not have major impairment in function or psychological distress. Symptoms often are based on gastrointestinal dysfunction (ie, vomiting, diarrhea, constipation), and pain is minimal or mild and without other comorbid physical symptoms. Patients with mild symptoms do not usually have dominant psychiatric diagnoses and their quality of life is good, but they may report concerns about the implications of their symptoms on their life. These patients do not make frequent medical visits and usually maintain normal activity levels without restriction. Here, treatment is directed toward the following

1. Education. Indicate that FGIDs are very real disorders in which the gastrointestinal system is overly responsive to a variety of stimuli such as food, hormonal changes, medication, and stress. Pain resulting from spasm or stretching of the gut, from a sensitive gut, or from both can be experienced anywhere in the abdomen and can be associated with other effects on gastrointestinal function leading to symptoms (eg, pain, nausea, vomiting, diarrhea). Both physiological and psychological factors interact to produce symptoms.
2. Reassurance. First elicit the patient's concerns and then respond to them. This is usually done after appropriate evaluation.
3. Diet and medication. Offending dietary substances (eg, lactose, fermentable oligo-, di-, and monosaccharides and polyols, caffeine, fatty foods, alcohol) and medications that adversely cause symptoms should be identified and reduced or eliminated. Sometimes a food diary is helpful.

**Moderate symptoms.** A smaller proportion of patients, approximately 30%–35%, seen in primary or secondary care report moderate symptoms and have intermittent disruptions in activity, for example, missing social functions, work, or school. They may identify a close relationship between symptoms and inciting events such as dietary indiscretion, travel, or distressing experiences. They may have more moderate abdominal pain and be more psychologically distressed than patients with mild symptoms. There may be several other medical or psychological comorbidities, and these patients may lose time from work or need to curtail usual functioning. For this group, additional treatment options are recommended.

1. Symptom monitoring. Keeping a symptom diary for 1–2 weeks encourages the patient's participation in treatment and sense of control over the illness. It may help to identify inciting factors such as dietary indiscretions, lifestyle factors, or specific stressors not considered previously.
2. Pharmacotherapy directed at specific symptoms. Medication can be considered for symptom episodes

that are distressing or that impair daily function. The choice of medication depends on the predominant symptoms. In general, prescription medications should be considered as ancillary to dietary or lifestyle modifications for mild chronic symptoms and used during periods of acute symptom exacerbation, or they may be required on a regular basis for symptoms of moderate or frequent severity.

3. Psychological treatments. Psychological treatments may be considered for motivated patients with moderate-to-severe GI symptoms and for patients with pain. It is more helpful if the patient can associate symptoms with stressors. These treatments, which include cognitive-behavioral therapy, relaxation, hypnosis, mindfulness, and combination treatments, help to reduce anxiety levels, encourage health-promoting behaviors, and provide the patient with greater responsibility and control in the treatment and in potentially improving pain tolerance. See the article *Biopsychosocial Aspects of FGIDs*, for more details.

**Severe symptoms.** Approximately 20%–25% of patients with FGIDs often seen in referral practices have severe symptoms and a smaller proportion have very severe and refractory symptoms. They often have a high frequency of associated psychosocial difficulties including anxiety, depression or somatization, personality disturbance, and chronically impaired daily functioning, and approximately 10% or more will have work disability. There may be a history of major loss or abuse, poor social networks or coping skills, and catastrophizing behaviors. These patients may see gastroenterology consultants frequently and may hold unrealistic expectations to be cured. Perhaps from earlier experiences in the health care system, they may feel stigmatized with their condition and deny or not consider a role for psychosocial factors in the illness. As a result, they may be unwilling to engage in psychological or psychopharmacologic treatment but more often will seek further diagnostic studies to legitimize their complaints and choose pharmacologic treatments directed at the gut. For this group, the following treatment options are recommended.

1. The physician's approach. In addition to the general 12-step approach previously described, the clinician also should: (a) perform diagnostic and therapeutic measures based on objective findings rather than in response to patient demands; (b) set realistic treatment goals, such as improved quality of life rather than complete pain relief or cure; (c) shift the responsibility for treatment to the patient by giving therapeutic options; and (d) change the focus of care from treatment of disease to adjustment to and management of chronic illness.
2. Antidepressant treatment. If pain is a dominant feature, tricyclic antidepressants (eg, desipramine, amitriptyline) or the serotonin-norepinephrine reuptake inhibitors (eg, duloxetine, milnacipran) help control pain via central analgesia as well as provide

relief of associated depressive symptoms. The selective serotonin reuptake inhibitors (eg, citalopram, fluoxetine, paroxetine) are less effective for pain but can help reduce anxiety and associated depression. Antidepressants should be considered for patients with chronic pain and impaired daily functioning, co-existent symptoms of major depression, symptom anxiety, or panic attacks. Even without depressive symptoms, these agents may help when the pain is dominant and consuming. For more information, see the articles entitled, "Biopsychosocial Aspects of FGIDs" and "Centrally Mediated Disorders of GI Pain."

3. Functional GI or pain treatment center referral. There are several GI programs and possibly pain treatment centers that provide a multidisciplinary approach to FGID management. Here, the team approach is directed toward pain management, improved coping skills, and overall rehabilitation of patients who have become disabled.

## Concluding Comments

In providing an overview of the functional GI disorders and the Rome Foundation process, we set the stage for the information to follow. A great deal has happened in the 10 years since the publication of Rome III. We believe that this new information will help the reader gain a better understanding of these disorders and improve the diagnosis and care of his or her patients. Rome IV is the culmination of a 6-year effort of 117 internationally recognized investigators and clinicians representing 23 countries along with 10 administrative staff and consultants. As we look back on the process, the information obtained is comprehensive, although there is still more to learn. When more advances in our understanding and treatment of these disorders occur in future years, we will revise the information again as we advance to Rome V. The Rome process is a dynamic one, and we look forward to future activities designed to help improve the science of FGIDs and care of the patients.

## Supplementary Material

Note: The first 50 references associated with this article are available below in print. The remaining references accompanying this article are available online only with the electronic version of the article. Visit the online version of *Gastroenterology* at [www.gastrojournal.org](http://www.gastrojournal.org), and at <http://dx.doi.org/10.1053/j.gastro.2016.02.032>.

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**Conflicts of interest**

The author discloses no conflicts.

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