



# What Is New in Rome IV

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Functional gastrointestinal disorders (FGIDs) are diagnosed and classified using the Rome criteria; the criteria may change over time as new scientific data emerge. The Rome IV was released in May 2016. The aim is to review the main changes in Rome IV. FGIDs are now called *disorders of gut-brain interaction (DGBI)*. Rome IV has a multicultural rather than a Western-culture focus. There are new chapters including multicultural, age-gender-women's health, intestinal microenvironment, biopsychosocial, and centrally mediated disorders. New disorders have been included although not truly FGIDs, but fit the new definition of DGBI including *opioid-induced gastrointestinal hyperalgesia*, *opioid-induced constipation*, and *cannabinoid hyperemesis*. Also, new FGIDs based on available evidence including *reflux hypersensitivity* and *centrally mediated abdominal pain syndrome*. Using a normative survey to determine the frequency of normal bowel symptoms in the general population changes in the time frame for diagnosis were introduced. For *irritable bowel syndrome (IBS)* only pain is required and discomfort was eliminated because it is non-specific, having different meanings in different languages. Pain is now related to bowel movements rather than just improving with bowel movements (ie, can get worse with bowel movement). Functional bowel disorders (*functional diarrhea*, *functional constipation*, *IBS with predominant diarrhea [IBS-D]*, *IBS with predominant constipation [IBS-C]*, and *IBS with mixed bowel habits*) are considered to be on a continuum rather than as independent entities. Clinical applications such as diagnostic algorithms and the Multidimensional Clinical Profile have been updated. The new Rome IV iteration is evidence-based, multicultural oriented and with clinical applications. As new evidence become available, future updates are expected.

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## Key Words

Constipation; Diarrhea; Functional gastrointestinal disorders; Irritable bowel syndrome; Rome IV

## Introduction

Functional gastrointestinal disorders (FGIDs) classification and diagnostic criteria began in the late 1980s, when a group of international experts were recruited by Professor Aldo Torsoli from Italy to develop Working Teams for the International Gastroenter-

ology meeting in Rome 1988. The purpose was to answer difficult questions using a consensus methodology through the Delphi approach about a group of gastrointestinal disorders that had little scientific-based evidence to understand etiology pathophysiology and treatment at the time. One committee was established to develop for the first time diagnostic guidelines for irritable bowel syndrome (IBS). This was chaired by Prof W Grant Thompson from Canada

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and published in 1989.<sup>1,2</sup> This IBS Working Team was the starting point for the Rome process that later generated consensus-based criteria for other disorders without an anatomical or structural basis. With the support of Dr Enrico Corazziari representing Dr Aldo Torsoli, Dr Douglas A Drossman, a member of the original IBS Working Team, set up another working team to create a classification system with diagnostic criteria for all of the FGIDs. The classification was divided into 5 anatomical regions including the esophagus, gastroduodenal tract, bowel, biliary tract, and anorectal area, and was published in *Gastroenterology International*.<sup>3</sup> A refinement of the classification system was made with a series of papers in the same journal by 5 additional working teams.<sup>3-7</sup> In all, there were criteria for 21 FGIDs and this led to the development of a research instrument to conduct an epidemiological survey used for the first US Householder Epidemiological Study,<sup>8</sup> a seminal paper in the field. These papers were further compiled in a book entitled “The functional gastrointestinal disorders: diagnosis, pathophysiology and treatment,” published in 1994.<sup>9</sup>

The birth of the Rome process and its classification system served as the basis for an incredible explosion of research in the field as well as to legitimize the patient’s having these symptoms.<sup>10</sup> However, with evolving science and new evidence, the Rome process became a dynamic one requiring updates leading to revisions in the

publications. Therefore, 28 years after the first Working Team on IBS, and 10 years after the last iteration of the Rome process (Rome III) were published, the Rome IV process and consequently the modified Rome IV classification and criteria have been published in a supplement of *Gastroenterology* as well as in a collection of books, both in hard copies and online, this past May 2016.<sup>11,12</sup>

This was accomplished by a rigorous process of prospective and retrospective data collection, synthesis, data discussion, group decision making, and peer-review.<sup>13</sup> Table 1 summarizes the Rome IV process.

### Rationale for a Symptom-based Classification

A FGID (eg, functional heartburn and IBS) relates to the patients’ interpretation and reporting of the illness experience, and it is classified primarily in terms of symptoms. A symptom is an experience perceived as different from normal, while a syndrome (eg, any of the FGID) is a consistent association of symptoms.<sup>13</sup> While a FGID may have an abnormal motility finding such as rapid intestinal transit in IBS patients with diarrhea (IBS-D)<sup>14</sup> or a pathologic finding such as increased in colonic mucosal mast cells,<sup>15</sup> these factors are neither sufficient nor necessary for defining

**Table 1.** The Rome IV Process

Years	Level	Actions
2008	Rome Foundation Board of Directors	Identified key areas to acquire preliminary knowledge for the Rome IV Chapter Committee
2010-2012	Rome Foundation Board of Directors	Creation of the Rome IV Editorial Board Members
	Rome IV Editorial Board Members	Identified Chairs and Co-chairs of the 18 committees
	Rome IV Committees Chairs and Co-chairs	Selection of committee members to produce Rome IV Chapters
	Rome Foundation Board of Directors	Creation of Support Committees to provide ancillary service to the chapter committees
2013 (May)	Rome Foundation Board of Directors	Orientation meeting
	Support Committees	Presented their work
2013-2015	Rome IV Committees	Critically synthesized the literature and created the requested documents through several revisions.
2014 (December)	Rome IV Committees	Meeting in Rome (Rome IV Conference) to revise the documents and established consensus on scientific content and diagnostic criteria
	Rome IV Editorial Board, Committee Chairs and Co-Chairs	Harmonization meeting to summarize and present their committees’ recommendation to the group
2015	Committee Chairs and Co-Chairs	Each document was sent out for peer-review by international experts
2015 (Autumn)	Committee Chairs and Co-Chairs and Members	Manuscripts for the Rome IV Gastroenterology supplements were created
	Rome IV Editorial Board	Reviewed the manuscripts for the Rome IV Gastroenterology supplements
	Rome IV Committee Members	Signed off on all documents before they were sent to copy editor for final check

a FGID. Thus, by moving from motility based categorization to a symptom based method we can identify underlying pathophysiological determinants, be they motility, hypersensitivity, or brain-gut dysfunction. This classification based on symptom groupings (developed by population cluster analysis and clinical studies) thus represent what patients bring to doctors. This approach opens the door for the study of additional pathophysiological processes. It is not coincidence that the growth in the work on visceral hypersensitivity and sensitization, brain-gut interactions, microbiota etc, began right at the time of the classification system published in 1990.<sup>16-19</sup> Because patients were selected for these studies based on symptom criteria which defined the cohorts. Other benefits include the ability of having homogeneous groups for clinical trials with the Food and Drug Administration (FDA) and European Medicines Agency endorsement of these criteria. This led to a marked increase in drug discovery and use.<sup>20-22</sup> Finally such a classification system provides legitimization for patients and doctors.

## A New Definition for Functional Gastrointestinal Disorders: Disorders of Gut-Brain Interaction

Although the word *functional* has been embedded in our terminology, there has been a longstanding discussion to eliminate this term because of the term being non-specific and potentially stigmatizing. Based on more recent scientific knowledge that proposes the interaction of multifactorial pathophysiological factors involved on the generation of these disorders, a revised definition was created: *disorders of gut-brain interaction (DGBI)* to help clarify its meaning. These disorders are defined as *a group of disorders classified by GI symptoms related to any combination of motility disturbances, visceral hypersensitivity, altered mucosal and immune function, gut microbiota, and/or central nervous system processing.* We will be using this new term throughout the article to represent FGIDs.

*Functional* has been removed from the chapters and article titles (for example *Gastroduodenal Disorders* instead of *Functional Gastroduodenal Disorders*) and from certain diagnoses when possible (for example *Fecal Incontinence* instead of *Functional Fecal Incontinence*). The Rome Foundation understands that it will take time until the term *functional* is completely eliminated from the health care language, and in some clinical disorders the term *functional* was retained to distinguish them from other similar disorders (for example *Functional Diarrhea*) until a more appropriate term can be used.<sup>13</sup>

## Multicultural Orientation

Traditionally, the Rome approach was based on Western knowledge to understand patients' symptoms, which has limitations for other countries and cultures.<sup>2,13</sup> Thus, one of the major changes in Rome IV is addressing these limitations by moving from a Western ethnocentric focus to a multi-cultural orientation. This could be uniquely accomplished through 117 experts from 23 countries as part of the Rome IV process. What resulted was the inclusion of a new chapter devoted entirely to multi-cultural information that addresses the global perspective on these disorders. This chapter, "Multi-cultural Aspects in Functional Gastrointestinal Disorders (FGIDs)"<sup>23</sup> was an extension of the Rome Foundation Working Team on Multinational, Cross-Cultural Research, which completed its work in 2014.<sup>24-26</sup> The chapter elaborated on a conceptual model relating to the interaction between culture and DGBI, focusing on patients, physicians, food and eating, and culture in symptom interpretation and clinical manifestations.<sup>27</sup> Culture defined as the values, beliefs, norms, and practices of a particular group that are learned and shared<sup>28</sup> can guide, thinking (eg, food taboos), decisions (eg, illness explanatory model), and actions (eg, treatment choice). Patients have symptoms or disease related beliefs that affect their concerns, anxieties, and expectations of the health care process known as explanatory models.<sup>29</sup> Although factors such as the cultural background, educational level, and sex can contribute to these explanatory models, we also recognize that local biologics including genetics, microbiome/post-infectious IBS, environmental hygiene, cytokines, and the effects of CNS, can impact on symptom generation, manifestation, and interpretation. Also considered were the explanatory models of illness that may impose a barrier to the physician-patient relationship; gender; family relationships that can have a significant effect on the illness experience of the patient; and last but not least, symptom reporting as this varies between groups.<sup>23,30</sup> The most characteristic issue in terms of symptom reporting is *bloating*, a term confined primarily to the English language but absent in Spanish or Italian.<sup>23</sup> Also, the differentiation of bloating from postprandial fullness imposes a linguistic and cultural issue. For example, in China, postprandial fullness is limited to the epigastrium while bloating refers to a sensation of gas that is present in most, if not the entirely all over the abdomen and can reflect abdominal discomfort. However, discomfort is another expression without a translation to many languages. Therefore, pictograms may have to be designed and validated in the future for conducting cross-cultural research.<sup>23,27</sup>

As for food, in most cultures it plays a prominent role in DGBI patient symptom attribution and reporting and cultural factors can have a negative or positive meaning to food such as nocebo or placebo properties. Finally, physicians need to be prepared to work in a multicultural milieu to address this issues and be aware of how can religion and culture can affect treatment modalities including Complementary and Alternative Medicine, which should be included in the Western type of treatments. Notwithstanding, the differences in healthcare systems can influence the diagnostic work-up and treatment itself.<sup>27</sup>

## New Chapters

Not only the previous Rome III chapter on “Gender, age, society, culture, and the patients perspective” was split to give rise to 2 new Rome IV chapters, the “Multicultural Aspects in Functional Gastrointestinal Disorders”<sup>23</sup> and “The Age, Gender, and Women’s Health,”<sup>31</sup> and also a new chapter entitled “The Intestinal Microenvironment and Functional Gastrointestinal Disorders,”<sup>32</sup> was added based on the increasing evidence supporting a role for luminal gut factors in the generation of DGBI such as IBS and functional dyspepsia.<sup>32</sup> They included the interaction between diet and products of digestions, enteric infections or infestation, the microbe-host interactions including the immune and metabolic responses and biliary acids among others. These factors can interact with the gut mucosa not only triggering a leaky barrier, but in the presence of a permeability abnormality may allow an amplification of signaling from the lumen to neural and immune pathways, generating functional gastrointestinal symptoms.<sup>33</sup>

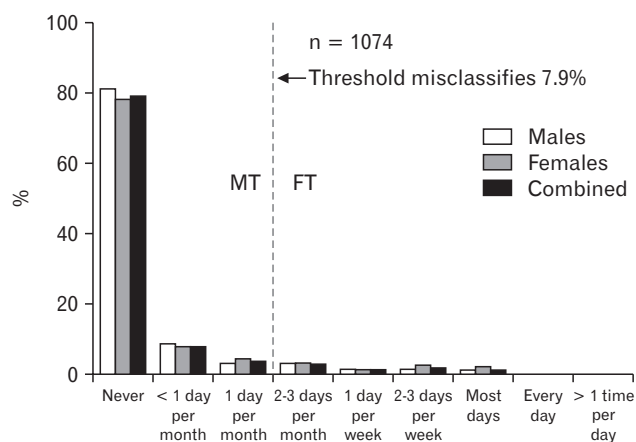
The “Psychosocial Aspects of Functional Gastrointestinal Disorders” chapter was changed to “Biopsychosocial Aspects of Functional Gastrointestinal Disorders”<sup>34</sup> to reflect the multi-determined nature of these processes. Finally the Rome III chapter on “Functional abdominal pain syndrome,” was changed to “Centrally Mediated Disorders of Gastrointestinal Pain” to reflect the range of gastrointestinal symptoms believed to have a central origin,<sup>35</sup> where central dysregulation of pain is the major contributor to the disorder.<sup>36</sup> The chapter includes the “Centrally mediated abdominal pain syndrome (CAPS)” resulting from central sensitization with disinhibition of pain signals rather than increased peripheral afferent excitability; and a new disorder called *narcotic bowel syndrome (NBS)* (see “New Disorders” section and “Diagnostic Criteria” section).<sup>36</sup>

## New Disorders

Rome IV has included new diagnoses that have a known etiology, yet they are included because they fit the new definition of DGBI, as related to their effects on altering the function of the CNS or enteric nervous system, and their clinical presentation is similar to DGBI, and the need to be readily recognized by clinicians. Also, they have not been fully accepted as discrete disorders nor have they been well characterized yet.<sup>13</sup> These new diagnoses include the *NBS (Opioid-Induced Gastrointestinal Hyperalgesia)* in the chapter, “Centrally Mediated Disorders of Gastrointestinal Pain”;<sup>36</sup> *Opioid Induced Constipation* in the chapter, “Bowel Disorders”;<sup>37</sup> and *Cannabinoid Hyperemesis Syndrome* in the chapter “Gastroduodenal Disorders.”<sup>38</sup>

## Threshold Changes: Normative Survey

Because there was limited information on the frequency of normal bowel symptoms in the general population, the Rome Foundation conducted a normative symptom study in a non-clinical sample in the USA, to be able to identify the prevalence of normalcy in order to statistically derive abnormal frequencies consistent with



**Figure 1.** Frequency of reporting of pain or burning above the belly button in the normative survey. The histograms show the frequency of reporting in different time frames for men, women and the combined sample. The vertical dotted line shows the 90th percentile for the combined sample of females and males. MT shows the minimum threshold in males and FT shows the minimum 90th percentile in females. Accordingly, a threshold of only 2-3 days a month would limit misclassification to 10% in females, whereas a threshold of 1 day/month would limit misclassification to 10% in males. Reproduced with permission from Rome Foundation, Inc.

DGBI.<sup>39</sup> The committee recommended the 90th percentile symptom frequency or men and women as the threshold to define normality.<sup>39</sup> For example, the presence of discomfort or pain anywhere in the abdomen was reported in the majority in the general population less than 2-3 days per month to never, and once a week or more for the combined sample occurred in 6.7%. Therefore, the frequency threshold for pain in IBS was set statistically at a minimum of once a week in Rome IV.<sup>37,39</sup> Another example is the frequency of pain or burning above the umbilicus, a cardinal symptom for functional dyspepsia depicted in Figure 1. The survey revealed differences in women and men. A threshold of 2-3 days a month was the threshold for women according to the 90th percentile, in contrast to 1 day a month in men. Although the frequency was less common in men than in women, in this case, it was decided to use the thresholds for the combined male and female sample because the differences were small between the 2 of them.<sup>40</sup> Furthermore, this higher frequency in women probably responds to an epidemiological phenomenon that explains why many functional gastrointestinal symptoms including uninvestigated dyspepsia are more frequent in women.<sup>41,42</sup>

## Changes in Diagnostic Criteria

The Rome IV categories and diagnoses for DGBI are listed in Table 2.<sup>11</sup> In the following section, we describe the changes and new diagnostic criteria that have been included in Rome IV from the upper to the lower digestive tract.

### Esophageal Disorders

With Rome III, functional heartburn was associated with no evidence for gastroesophageal reflux.<sup>43</sup> However, with the addition of impedance to esophageal pH monitoring it has been shown that 38% patients did not have acid reflux (pH-), yet had a positive symptom association based on the symptom associated probability (SAP+), in other words they had esophageal hypersensitivity with only 29% having true functional heartburn (pH-/SAP-).<sup>44</sup> Therefore, a new diagnosis was included, *reflux hypersensitivity*, defined by the presence of acid sensitivity in the absence of increased acid reflux.<sup>45</sup>

It must be noted that *reflux hypersensitivity* can overlap with true gastroesophageal reflux disease that can be identified in patients with known prior pathological reflux or erosive esophagitis in which reflux parameters (number of reflux events and acid exposure) are documented to have normalized on pH-impedance testing on proton pump inhibitors.<sup>45</sup>

### Gastroduodenal Disorders

*Functional dyspepsia (FD)* remains as an umbrella term referring to patients with *postprandial distress syndrome (PDS)* and *epigastric pain syndrome (EPS)*.<sup>38</sup> In general, PDS is a postprandial syndrome while EPS is not. However, pathophysiological studies investigating the effect of meal ingestion on symptom generation demonstrated that not only postprandial fullness and early satiety but also, epigastric pain or burning and nausea may increase after meal ingestion.<sup>46</sup> In other words, they can overlap. Therefore, the definition of PDS acknowledges that besides postprandial fullness and early satiety, patients may perceive epigastric pain and/or burning after meals.<sup>38</sup> Also, bloating, belching, and nausea can be present both in PDS and EPS, but vomiting is unusual.

Secondly, in Rome III a diagnosis of FD could be made with no minimum frequency of occurrence required. However, based on the normative survey, Rome IV now require a minimum frequency of occurrence for the dyspeptic symptoms (ie, postprandial fullness, early satiation, epigastric pain, and epigastric burning) before a diagnosis of FD is made (see above in “Normative Survey”) (Fig. 1).

Third, other minor changes included severity identified at least as *bothersome* (severe enough to impact on daily activities).<sup>38</sup> For research purposes, bothersome can be semi-quantitatively defined as  $\geq 2$  (ie, severe enough to at least distracting from usual activities) in a 5 point-scale to the effect exerted by symptoms on usual activities.

Chronic idiopathic nausea and functional vomiting syndrome were 2 separate entities in Rome III.<sup>47</sup> However, because of the lack of evidence to support different diagnostic investigations and treatments for these disorders, and the observation that both symptoms commonly coexist, Rome IV delineated a combined diagnosis called *chronic nausea vomiting syndrome*.<sup>48</sup> Notwithstanding, it was recognized that patients may present only with nausea or vomiting.<sup>48</sup>

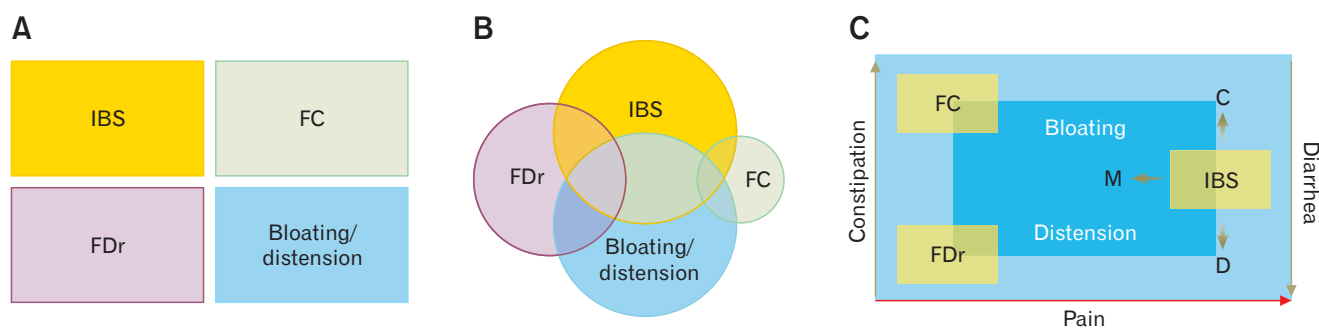
### Bowel Disorders

Previous versions of Rome considered functional bowel disorders such as IBS, functional diarrhea, functional constipation, and functional distension (Rome I) as separate entities. Later it was recognized that these disorders could overlap (Rome II-Rome III). However, in the clinic it may be not be possible to confidently separate disorders into separate entities. Such is the case of IBS with predominant constipation (IBS-C) from functional constipation or IBS-D from functional diarrhea. Thus, Rome IV considers that these disorders exist as a continuum rather than as in isolation (Fig. 2).<sup>49</sup> Furthermore, it is recognized that bloating and/or distension are common symptoms frequently reported by patients with any

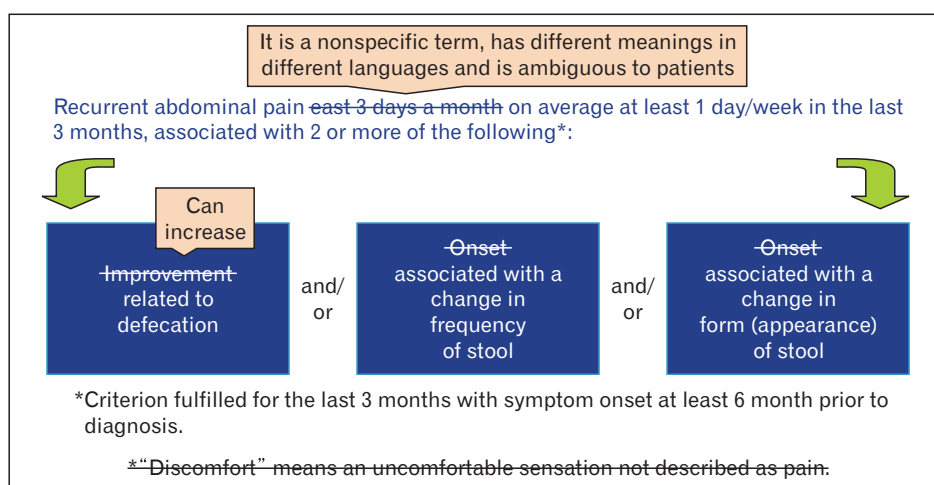
**Table 2.** Rome IV Classification of the Functional Gastrointestinal Disorders—Disorders of Gut-Brain Interaction

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	B3a. Chronic nausea vomiting syndrome
B1b. Epigastric pain syndrome	B3b. Cyclic vomiting syndrome
B2. Belching disorders	B3c. Cannabinoid hyperemesis syndrome
B2a. Excessive supragastric belching	B4. Rumination syndrome
B2b. Excessive gastric belching	
C. Bowel disorders	
C1. Irritable bowel syndrome	C2. Functional constipation
IBS with predominant constipation	C3. Functional diarrhea
IBS with predominant diarrhea	C4. Functional abdominal bloating/distension
IBS with mixed bowel habits	C5. Unspecified functional bowel disorder
IBS unclassified	C6. Opioid-induced constipation
D. Centrally mediated disorders of gastrointestinal pain	
D1. Centrally mediated abdominal pain syndrome	D2. Narcotic bowel syndrome/opioid-induced gastrointestinal hyperalgesia
E. Gallbladder and sphincter of Oddi disorders	
E1. Biliary pain	E2. Functional pancreatic sphincter of Oddi disorder
E1a. Functional gallbladder disorder	
E1b. Functional biliary Sphincter of Oddi disorder	
F. Anorectal disorders	
F1. Fecal incontinence	F3. Functional defecation disorders
F2. Functional anorectal pain	F3a. Inadequate defecatory propulsion
F2a. Levator ani syndrome	F3b. Dyssynergic defecation
F2b. Unspecified functional anorectal pain	
F2c. Proctalgia fugax	
G. Childhood functional gastrointestinal disorders: neonate/toddler	
G1. Infant regurgitation	G5. Functional diarrhea
G2. Rumination syndrome	G6. Infant dyschezia
G3. Cyclic vomiting syndrome	G7. Functional constipation
G4. Infant colic	
H. Childhood functional gastrointestinal disorders: child/adolescent	
H1. Functional nausea and vomiting disorders	H2. Functional abdominal pain disorders
H1a. Cyclic vomiting syndrome	H2a. Functional dyspepsia
H1b. Functional nausea and functional vomiting	H2a1. Postprandial distress syndrome
H1b1. Functional nausea	H2a2. Epigastric pain syndrome
H1b2. Functional vomiting disorders	H2b. Irritable bowel syndrome
H1c. Rumination syndrome	H2c. Abdominal migraine
H1d. Aerophagia	H2d. Functional abdominal pain - not otherwise specified
	H3. Functional defecation
	H3a. Functional constipation
	H3b. Non-retentive fecal incontinence





**Figure 2.** Different models to explain functional bowel disorders of gut-brain interaction. (A) Rome I considered the functional bowel disorders as different and independent entities. (B) Later, Rome II-Rome III recognized that these disorders could overlap between the different functional bowel disorders. (C) Rome IV now considers that bowel disorders exist on a continuum rather than independent disorders. Adapted and reproduced from Whorwell et al<sup>35</sup> with permission from Rome Foundation, Inc. IBS, irritable bowel syndrome; FC, functional constipation; FDr, functional diarrhea; C, constipation; D, diarrhea; M, mixed.



**Figure 3.** Changes in diagnostic criteria for irritable bowel syndrome (IBS) from Rome III to Rome IV. In Rome IV abdominal ‘discomfort’ has been deleted from the definition because of the imprecise nature of the term together with the fact that ‘discomfort’ is not present in every language; abdominal pain should be present at least 1 day a week on average during the preceding 3 months; ‘Improvement with’ defecation has been changed to ‘Related to’ defecation as in a subgroup of patients it may increase or remain without changes; and ‘Onset’ has been deleted from the associated changes in frequency and change in form (appearance) of stools. Adapted from Longstreth GF et al<sup>53</sup> and Mearin F et al.<sup>49</sup>

functional bowel disorder.<sup>49</sup>

*Irritable bowel syndrome* is the most commonly recognized DGBI around the world, notwithstanding its prevalence remains elusive due to the different diagnostic criteria and survey methods used in research studies.<sup>50</sup> However, Rome IV has introduced changes in the diagnostic criteria based on the available evidences,<sup>51</sup> as well as on the normative survey.<sup>39</sup> Firstly, the term discomfort included in the Rome III criteria is now eliminated from the new Rome IV criteria because a previous study showed that asking about discomfort is nonspecific and should be avoided in future Patient reported outcomes. Also, discomfort has different meanings in different languages and is an ambiguous term to patients.<sup>51</sup> Thus,

only abdominal pain is now included. Based on the Rome normative survey, pain should be present at least 1 day per week during the previous 3 months. As mentioned before, this was supported by the fact that according to the 90th percentile a lower frequency of pain was common in the general population.<sup>39,40</sup> In addition, in Rome III, pain or discomfort had to improve with defecation although in many patients, pain increases with defecation or it remains without changes.<sup>52</sup> Also, in Rome III, pain or discomfort onset had to be related with the other 2 criteria: onset associated with a change in frequency of stools; onset associated with a change in form (appearance) of stool.<sup>53</sup> Because not in every patient abdominal pain coincided with these changes in stools, onset is now deleted

from Rome IV.<sup>37</sup> The changes in IBS criteria from Rome III to Rome IV are depicted in Figure 3. It is important to acknowledge that in the first population-based study using Rome IV criteria in English speaking populations, the IBS prevalence decreased by half compared to that with Rome III criteria: 11.1% vs 6.1%, 11.7% vs 5.8%, and 10.6% vs 5.5% in the US, Canada, and the UK, respectively. It is possible that this change is related to the elimination of discomfort from the criteria.<sup>54</sup> Also, it is worth mentioning that in other areas like in Asia, patients do differentiate between pain and discomfort and although expressions such as bloating posed difficulty in translatability, bloating is more common than abdominal pain, and patients often report relief of their fullness or bloating with the passage of either stool or flatus.<sup>55</sup> Therefore, Rome IV criteria for IBS may need to be adapted in the future for other cultures as the data accumulates using these criteria.

In terms of IBS subtypes, IBS is mainly classified according to the predominant bowel habit for IBS-C, IBS-D, IBS with mixed bowel habits, and unclassified IBS.<sup>53</sup> In Rome IV, bowel habits are based on stool forms only during days with abnormal bowel movements (more than one-fourth: 25% of bowel movements).<sup>37</sup> This is in contrast to Rome III in which the 25% threshold was determined based on the total number of bowel movements irrespective of whether they were normal or not.<sup>53</sup> In fact this led to a predominance of unsubtyped IBS using Rome III as it was the case in several epidemiological studies the USA and Latin America.<sup>56-58</sup> The Rome IV IBS subtypes criteria<sup>49</sup> are depicted in Table 3.

*Functional abdominal bloating/distension* is diagnosed when either abdominal bloating (subjective) and/or distension (objective/visible increase in abdominal girth) predominate over other symptoms.<sup>49</sup> The addition of distension also reflects the findings with new technologies such as abdominal plethysmography.<sup>59</sup> Rome IV recognizes that patients may also report symptoms of mild abdominal pain and/or minor bowel movement abnormalities.

*Opioid induced constipation (OIC)* is one of the new disorders now included in Rome IV.<sup>49</sup> It has a prevalence of 41% in patients with chronic non-cancer pain, and up to 94% of patients taking opi-

oids for cancer-related pain.<sup>60</sup>

Initial treatment of OIC is similar to that of functional constipation including laxatives and lubiprostone has been approved by FDA for patients with OIC in patients with non-cancer pain.<sup>61</sup> Also, opioid receptors antagonists such as naloxone and naltubuphine that are centrally active, can be used but may be related with withdrawal symptoms. Recently, peripherally acting  $\mu$ -opioid antagonists (PAMORAs) that block the opioid receptors in the gastrointestinal tract but not centrally, have been developed.<sup>62</sup>

### Centrally Mediated Disorders of Gastrointestinal Pain

This category includes 2 disorders, *centrally mediated abdominal pain syndrome*, formerly in Rome III, functional abdominal pain syndrome, and the new *narcotic bowel syndrome/opiate induced hyperalgesia*.<sup>36</sup>

*Centrally mediated abdominal pain syndrome* can be distinguished from other DGBI by its strong central component and relative independence from motility disturbance or evidence for visceral hypersensitivity. It results from central sensitization with disinhibition of pain signals rather than increased peripheral afferent excitability.<sup>36</sup> Symptom related behavior in patients with CAPS that can facilitate their identification include the expression of pain of varying intensity though verbal and nonverbal methods, urgent reporting of intense symptoms, minimizing a potential role for psychosocial contributors, frequently seeking for health care, request for narcotic analgesics, focusing their attention on complete symptom relief, taking limited personal responsibility for self-management, and requesting diagnostic studies.<sup>35</sup> CAPS is typically associated with psychiatric comorbidity, but there is no specific profile that can be used for diagnosis, and some degree of gastrointestinal dysfunction may be present.<sup>35</sup>

The management of CAPS relies on a strong patient-physician relationship, early incorporation of non-pharmacological therapies, and referral behavioral health therapies when needed.<sup>63</sup> The later ones can include psychodynamic interpersonal psychotherapy,

**Table 3.** Rome IV Irritable Bowel Syndrome-Subtypes Criteria

IBS Subtype	Criteria
IBS-C	More than one-fourth (25%) of bowel movements with Bristol Stool Scale Types 1-2 and less than one-fourth (25%) with Types 6-7.
IBS-D	More than one-fourth (25%) of bowel movements with Bristol Stool Scale Types 6-7 and less than one-fourth (25%) with Types 1-2.
IBS-M	More than one-fourth (25%) of bowel movements with Bristol Stool Scale Types 1-2 and more than one-fourth (25%) with Types 6-7.
IBS-U	Patients meet diagnostic criteria for IBS but their bowel habits cannot be accurately categorized in any of the above subtypes.

IBS, irritable bowel syndrome; IBS-C, IBS with predominant constipation; IBS-D, IBS with predominant diarrhea; IBS-M, IBS with mixed bowel habits; IBS-U, unclassified IBS.



hypnotherapy, mindfulness, and cognitive behavioral therapy. As for pharmacological therapies, low dose tricyclic antidepressants or serotonin-norepinephrine reuptake inhibitors can be used along with the general measurements.<sup>36</sup> These medications are initially used for 4–6 weeks and doses can be increased in case of incomplete response for another similar period. If necessary, an *augmentation* protocol, that is a combination of 2 or more treatments usually at lower dosages, that act at different receptor sites or areas of the brain may be used to enhance the therapeutic effect.<sup>64</sup>

*Narcotic bowel syndrome/opiate induced-gastrointestinal hyperalgesia* is characterized by the paradoxical development of, or increases in, abdominal pain associated with continuous or increasing dosages of opioids.<sup>65</sup> NBS can occur in patients with DGBI, chronic organic gastrointestinal diseases, and painful malignant or non-malignant diseases.<sup>35</sup>

Treatment includes understanding and helping to modify the patients' belief that narcotics are all that can help them; a sound patient-physician relationship and education of the patient about the treatment including opiate detoxification which provides a success rate of 89.7%. A detoxification protocol has been described elsewhere.<sup>66</sup>

## Gallbladder and Sphincter of Oddi Disorders

This category includes *biliary pain*, *functional gallbladder disorder*, and *functional biliary sphincter of Oddi disorder*.<sup>67</sup> Biliary pain can occur in the absence of recognized organic causes and some patients are cured by removal of the gallbladder or ablation of the sphincter. In terms of criteria changes for biliary pain disorder from Rome III to Rome IV is only in quantifying the pain. That is *not significantly* (< 20%) related to bowel movements and/or relieved by postural change or acid suppression. In addition, the occurrence of the pain should not be daily, although this is not evidence based.<sup>67</sup>

The other changes that have been introduced in Rome IV are in relation to *functional biliary sphincter of Oddi disorder*. Dysfunction of the sphincter of Oddi (SOD) is commonly considered in patients with biliary-type pain after cholecystectomy, and has been traditionally classified in 3 clinical types of SOD based on manometry and relief with sphincterotomy.<sup>67</sup> However, a recent NIH study (EPISOD: evaluating predictors and interventions in sphincter of Oddi dysfunction) has shown that true sphincterotomy is no better than sham sphincterotomy in patients with post-cholecystectomy pain, so that the old concept of SOD Type III is now considered more like functional than biliary related, and endoscopic retrograde cholangiopancreatography approaches are no longer appropriate in

that context.<sup>68</sup> Furthermore, most patients with SOD Type I have organic stenosis (eg, stones, stricture, pancreatitis, and pancreatic tumor) rather than motility disturbance of the sphincter; and biliary sphincterotomy is recommended; however not in this biliary classification. Therefore, Rome IV now recommends using the term suspected *functional biliary sphincter of Oddi disorder* for patients with prior SOD Type II only.<sup>67</sup>

Normal amylase/lipase levels may occur in some pain episodes.<sup>67</sup> Also, abnormal biliary manometry was added to the supportive criteria as it has been shown to be a predictor of response to biliary sphincterotomy,<sup>69</sup> and hepatobiliary scintigraphy was also included although its value is disputed.<sup>67</sup>

## Anorectal Disorders

Subtle changes were made in this category for Rome IV.<sup>70</sup> For Functional Fecal Incontinence, the diagnosis has been changed to a generic one, *fecal incontinence*.<sup>70</sup> In Rome III, chronic proctalgia was subcategorized into levator ani syndrome, unspecified anorectal pain, and proctalgia fugax. Rome IV has retained these three subcategories but has deleted chronic proctalgia as it may include many other conditions.<sup>70</sup> Also, the location of pain in *proctalgia fugax* has been revised to the *rectum* instead of anal canal or lower rectum.<sup>70</sup>

Regarding the *functional defecation disorders*, in the previous classification only patients with functional constipation would be eligible to be diagnosed with a defecatory disorder. However, because it has been recognized that patients with IBS and pelvic floor dysfunction can have an association with dyssynergic dysfunction,<sup>71</sup> and they can be treated with biofeedback irrespective of their association with IBS,<sup>72</sup> IBS-C have now been included in the Rome IV definition.<sup>70</sup> In addition, criteria for inadequate propulsive forces and inappropriate contraction of the anal sphincter and/or pelvic floor muscles are no longer specified because they vary among different techniques.<sup>72-74</sup>

In patients with functional defecation disorders, the following subcategories apply: *inadequate defecatory propulsion* defined by inadequate propulsive forces as measured with manometry with or without inappropriate contraction of the anal sphincter and/or pelvic floor muscles; and *dyssynergic defecation* defined by inappropriate contraction of the pelvic floor as measured with anal surface electromyography or manometry with adequate propulsive forces during attempted defecation.<sup>70</sup>

## Childhood Functional Gastrointestinal Disorders

In the last decade, new insights have been gained about the different DGBI in “neonate/toddlers” and “child/adolescents.” The

**Table 4.** The Multidimensional Clinical Profile Categories

Categories	Examples
A. Categorical diagnosis based on Rome IV criteria	
B. Clinical modifiers	Bowel habit predominance (ie, IBS-D, IBS-C, IBS-M), post-infection (PI), gluten sensitivity, FODMAPs sensitivity
C. Severity impact by self-perception	Mild, moderate, severe
D. Psychosocial modifiers and comorbidities	Can be categorical (eg, DSM Axis I), dimensional (eg, HADS, psychosocial red flags), or patient reported (eg, abuse)
E. Physiological modifiers and biomarkers of clinical relevance that enhance understanding of the diagnosis	eg, motility, biochemical, antibodies

IBS-C, IBS with predominant constipation; IBS-D, IBS with predominant diarrhea; IBS-M, IBS with mixed bowel habits; FODMAPs, fermentable oligo-, di-, monosaccharides, and polyols; HADS, Hospital Anxiety and Depression Scale; DSM, Diagnostic and Statistical Manual of Mental Disorders.

current criteria are based more on evidence and less on the experts' experience. DGBI in "neonates and toddlers" include: infant regurgitation, infant rumination syndrome, cyclic vomiting syndrome, infant colic, functional diarrhea, infant dyschezia, and functional constipation.<sup>75</sup> Main changes have been introduced in *infant colic* that has been expanded to include criteria for the general pediatrician and specific criteria for researchers. Also, a section on Neurobiology of Pain in infants and toddlers has been added that addresses the neurodevelopment of nociception and of the wide array of factors that may impact the experience of functional pain. This is contrary to the explanation of the acute pain model that if the pathology of pain is addressed, the pain will dissipate.<sup>75</sup>

In the "child/adolescent" section, based on the available evidence, the statement "no evidence for organic disease" has been removed from every definition and is now replaced for "after appropriate medical evaluation the symptoms cannot be attributed to another medical condition."<sup>76</sup> *Functional nausea and functional vomiting* has now been included and in *functional dyspepsia*, the *PDS* and *EPS* subtypes which were not present in Rome III, have now been adopted. Also, the Rome III *functional abdominal pain* and *functional abdominal pain syndrome* has now been substituted for *Functional Abdominal Pain-Not Otherwise Specified*. The frequency required for pain is changed from weekly to 4 times/month to align with other *functional abdominal pain disorders (FAPD)* and to allow for the inclusion of children who would otherwise not qualify for FAPD. In addition, the wording "that does not occur solely during physiologic events (eg, eating, menses)" has been added to harmonize with the adult criteria. Finally, it has been recognized that DGBI can coexist with other medical conditions such as inflammatory bowel disease.<sup>76</sup>

## Clinical Applications and Resources: Clinical Algorithms, the Multidimensional Clinical Profile, Interactive Clinical Decision Toolkit, and Primary Care

Although the Rome criteria are very useful for clinical research and pharmaceutical trials, they have limitations in clinical practice, as many of our patients do not fulfill all the criteria or the necessary time frame to be diagnosed (sub-threshold disorders), however they would receive equivalent treatments.

"The Rome IV diagnostic algorithms for common gastrointestinal disorders" have been published to meet clinical standards in diagnostic evaluation since the publication of the previous edition 6 years before, and to be consistent with the new Rome IV diagnostic criteria.<sup>77</sup> An updated set of diagnostic approaches beginning with common symptoms (eg, abdominal pain, nausea, diarrhea, and constipation) leading to diagnostic testing and ending with diagnosis, is provided. This would be the first part of the clinicians decision in making a diagnosis, and this would be followed by treatment.<sup>77</sup>

Furthermore, the Multidimensional Clinical Profile (MDCP) has been developed to capture the full dimension of each patient's clinical presentation and therefore planning an individualized treatment, and is also updated for Rome IV,<sup>78</sup> The MDCP is probably the first attempt to a Personalized Medicine approach in the field of DGBI. The MDCP comprises of five categories depicted in Table 4.<sup>78</sup> The Rome IV MDCP book included 72 cases to enhance the learning about DGBI and the influence of physiological and psychological factors contributing to the patients clinical presentation. Pediatric and multicultural cases have been included as well.<sup>79</sup>

Rome has created the Rome IV Interactive Clinical Decision Toolkit, an intelligent software system that addresses the sophistication and complexity of DGBI diagnosis and treatment protocols

by providing an online resource to assist practitioners in achieving optimal clinical outcomes. It offers a powerful online and interactive approach for accessing the combination of the Rome IV Diagnostic Algorithms and the MDCP treatment guidelines on-demand and at the point of care. This software will provide both an educational resource as well as a daily guideline to the patients' individualized diagnosis and treatment. Using any browser-enabled device, physicians and clinicians interact visually with Rome algorithms and guidelines, seeing all relevant decision pathways developed from actual clinical cases and using touch inputs to highlight and activate the pathways that lead to the optimal outcomes and recommendations. The platform operates in the ways that clinicians need to work: by using a logical, multidimensional and yet individualized framework for proper decision making.

Rome IV has also published "The pediatric functional gastrointestinal disorders" book and "The diagnostic questionnaires and tables for investigators and clinicians" book. Finally, recognizing that DGBI are ever present and disorders such as IBS are one of the main reasons for consultation in primary care, Rome IV has published a handbook to help busy primary care physicians on how to diagnose and managed the most common DGBI seen at this level of healthcare.<sup>80</sup>

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