

Irritable bowel syndrome: what do the new Rome IV diagnostic guidelines mean for patient management?

William E. Whitehead^a, Olafur S. Palsson^a and Magnus Simrén^{a,b}

^aDivision of Gastroenterology Hepatology, Centre of Functional Gastrointestinal & Motility Disorders, University of North Carolina Chapel Hill, Chapel Hill, NC, USA; ^bGastroenterology, Sahlgrenska University Hospital, Gothenburg, Sweden

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1. Introduction

The Rome criteria are universally used as inclusion criteria in pharmaceutical clinical trials and have therefore contributed to testing of several irritable bowel syndrome (IBS)-specific drugs. However, clinicians do not routinely use them because they are complex and consequently difficult to remember. Revised Rome diagnostic criteria for IBS and other functional gastrointestinal disorders (FGIDs) were published in May 2016 [1]. These revised criteria, referred to as the Rome IV criteria, replace the Rome III diagnostic criteria published 10 years earlier. Changes to the diagnostic criteria raise a number of questions both for clinicians and clinical researchers which will be addressed in this review:

- (1) Why revise the Rome III criteria now?
- (2) Are the new criteria validated?
- (3) What are the differences between Rome III and Rome IV?
- (4) How will these changes affect patient management?

2. Why revise the Rome III criteria now?

The Rome III criteria for IBS performed relatively well and were widely accepted around the world; why change them now? In fact only small changes, detailed below, were made in the IBS diagnostic criteria. In part, they were made to address important questions that have been raised about (1) the inclusion of abdominal 'discomfort' as an alternative to pain [2], (2) the most appropriate frequency of pain for IBS classification, and (3) the way Rome III dealt with the comorbidity of constipation-predominant IBS (IBS-C) with functional constipation [3,4]. It is also important to update clinicians on the explosion of new information on the pathophysiology of IBS (e.g. recognition that IBS is a brain-gut disorder and recognition of the role of gut microflora, intestinal permeability, and inflammatory signaling pathways to symptom development) and the new treatment options (e.g. linaclotide, rifaximin, eluxadoline, and low fermentable oligosaccharides, monosaccharides, and polyols diets) that have come out in the last decade. Although the

changes to the IBS diagnostic criteria appear to be minor, they will have a substantial impact on whether patients with less-frequent symptoms are diagnosed IBS.

3. Validation of the Rome IV diagnostic criteria

A frequent criticism of the Rome III diagnostic criteria was that they were not adequately validated; consequently, special attention was paid to validating the Rome IV criteria prior to publication [5]. The Rome Foundation sponsored a series of studies to address different aspects of clinical validation which are summarized below.

3.1. Evidence-based thresholds for symptom frequency

Diagnosis of IBS relies on symptoms (e.g. abdominal pain and altered stool frequency) that also occur in healthy individuals; these symptoms are not clinically significant unless they occur at an abnormal frequency or intensity. However, the frequency with which these symptoms occur in the population was not known, and the thresholds included in the Rome III criteria were based on expert opinion. To address this, the Rome Foundation surveyed the frequency of occurrence of these and other FGID symptoms in a nationally representative sample of 1665 US adults stratified by sex, age, and race [5]. Frequency histograms were computed for each symptom, and the 90th percentile was chosen as the threshold for clinical significance. The Rome working teams tasked with revising the Rome diagnostic criteria were encouraged to use these evidence-based thresholds, and this resulted in a change in the frequency of abdominal pain required for IBS diagnosis from 3 days per month to once per week.

3.2. Clinical validation

In the absence of a biological marker for IBS, symptom criteria have been validated against one of two reference standards: a negative endoscopy in a patient with abdominal pain or a clinical diagnosis made by an experienced clinician following any medical tests they required to exclude alternative diagnoses [6]. The Rome IV criteria were validated against a hybrid

Table 1. Diagnostic accuracy of Rome IV compared to Rome III criteria.

Test statistic	Rome IV	Rome III
Sensitivity	.627	.731
Specificity	.971	.931
Positive likelihood ratio (PLR) ^a	21.6	10.6
Negative likelihood ratio (NLR) ^b	.384	.289

^aThe PLR is defined as sensitivity/(1-specificity) [7]. Larger numbers reflect a greater likelihood that a positive finding on the diagnostic test is associated with true disease.

^bThe NLR is defined as (1-sensitivity)/specificity. Smaller numbers reflect greater likelihood that a negative finding on a diagnostic test is associated with absence of disease.

of these two approaches; a total of 843 patients were recruited by experienced gastroenterologists at nine academic medical centers in three countries. Enrollment was targeted at patients with established clinical diagnoses of the three most common FGIDs: IBS, functional constipation, and functional dyspepsia. The resulting sample included 427 patients with a primary clinical diagnosis of IBS. Only after the completion of their work-up and assignment of a diagnosis of IBS were patients directed to a website to complete the Rome IV diagnostic questionnaire plus the Rome III diagnostic questions for IBS. These patients were required to have had a negative colonoscopy within 5 years. This enabled us to estimate the sensitivity of the Rome IV criteria and to compare this to the performance of Rome III in the same patients. Results are shown in Table 1 where it can be seen that the Rome IV criteria, by comparison to the Rome III criteria, correctly identify a somewhat lower percent of the patients diagnosed IBS by expert clinicians (sensitivity), but they are less likely to identify a person incorrectly as having IBS (specificity). Future analyses will test whether the patients who would be identified by Rome III but not Rome IV have milder as well as less frequent symptoms.

3.3. Performance of the Rome IV criteria in a population-based sample

We next surveyed representative population samples of approximately 2000 people from the United States, United Kingdom, and English-speaking parts of Canada. The combined final sample was 5931 individuals. This allowed us to estimate the prevalence of IBS and the specificity of the diagnostic criteria in an unbiased sample. The estimated prevalence of IBS was substantially lower when using the Rome IV criteria (5.7%) as compared to the Rome III criteria (10.7%). Specificity of the Rome IV criteria was greater than Rome III (Table 1).

3.4. Test-retest reliability, understandability, and translatability of Rome IV

The Rome IV diagnostic questionnaire resulted in the same FGID diagnosis in 3/4 of patients over a 30-day period. Assessment of understandability of the diagnostic questionnaire in an independent sample of 532 community subjects stratified by age and educational level showed that more than

90% of individuals are likely to understand the questions without difficulty, and understandability ratings were found to be unrelated to age or education.

4. Specific changes to the Rome criteria and their consequences

- (1) Rome IV requires that abdominal pain occurs on average at least 1 day a week whereas only 3 days per month were required in Rome III. This was the most important factor accounting for a reduction in the estimated prevalence of IBS from 11.7% for Rome III to 5.7% for Rome IV [5]. The comorbidity of IBS with functional constipation, functional diarrhea, and functional dyspepsia also contributed to misclassifications [5].
- (2) Rome III allowed for a diagnosis of IBS on the basis of abdominal 'discomfort or pain' whereas Rome IV requires that patients have abdominal pain. The reasons for this change are (a) 'discomfort' is an ambiguous term which is interpreted by some patients as mild pain while others regard it as qualitatively different symptom such as urgency or bloating and (b) eliminating discomfort from the criteria brings the diagnostic criteria into closer alignment with the US FDA's guidance on evaluating IBS [2]. This change, requiring that pain be present, did not contribute significantly to the reduction in prevalence of IBS from Rome III to Rome IV.
- (3) The temporal association between abdominal pain and defecation or stool characteristics is less specific in Rome IV. (a) In Rome III abdominal pain had to improve following defecation whereas Rome IV only requires that abdominal pain is associated in time with defecation, that is, occurring either just before, during, or soon after defecation. (b) In Rome III changes in the frequency or consistency of stools had to follow the onset of abdominal pain, but in Rome IV these symptoms just have to be temporally associated. These changes in the temporal relationship between pain and defecation were also found to have little impact on the estimated prevalence of IBS.

In Rome III, the division of IBS into diarrhea-predominant (IBS-D), IBS-C, mixed (IBS-M), and unspecified (IBS-U) subtypes was based on the proportion of All bowel movements (BMs) that were loose/watery or hard/lumpy. However, subsequent studies showed that IBS subtyping was more reliable if based only on the proportion of abnormal BMs that were loose/watery or hard/lumpy [8] and this was adopted for Rome IV. In clinical practice and for epidemiological studies, Rome IV assigns the IBS subtype based on the patient's perception of their predominant type of abnormal stool consistency, resulting in a reduction in the number of patients who could not be classified (IBS-U) and the number who were classified IBS-M by the Rome III criteria. This affects clinical management because several medications are approved by the FDA only for the treatment of IBS-C (e.g. lubiprostone and linaclotide) while other medications are approved only for IBS-D (e.g. rifaximin and eluxadoline); and none are approved for the treatment of IBS-M or IBS-U.

5. Summary: implications of Rome IV for clinical management of IBS

The Rome IV criteria for diagnosing IBS are more restrictive than Rome III, primarily because they require more frequent abdominal pain than the older criteria. A major strength is that Rome IV criteria have been thoroughly validated and found to have adequate sensitivity and excellent specificity, to be reproducible over a 30-day interval, and the diagnostic questions are understandable to at least 90% of individuals of all ages and educational backgrounds. These revisions in the symptom criteria for IBS are likely to improve the performance of the Rome criteria for selecting more homogeneous groups of research subjects for clinical trials, but their use in routine clinical practice may still be perceived as burdensome due to their complexity. More widespread use of Rome IV criteria by clinicians may however be on the horizon, as the Rome Foundation is currently developing internet aides for easy administration and interpretation of the Rome IV criteria at the point of care. A limitation of the Rome IV criteria is that they remain exclusively based on symptom reports and a limited number of tests to exclude other diseases. This may gradually change as research efforts to identify biomarkers for IBS pay off, but at present there are no biomarkers that perform better than the Rome symptom criteria [9].

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Declaration of interest

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