Press Briefing
Functional Gastrointestinal Disorders

Introduction from the UEG Vice-President:
Paul Fockens

What’s New for Rome IV?:
Douglas Drossman

Breakthrough for IBS Patients:
Sean Bennet

Questions and Close:
Paul Fockens
What’s new for Rome IV

Douglas A. Drossman, MD
President, Rome Foundation
www.romecriteria.org
Rome Foundation Mission

*To improve the lives of people with Functional GI Disorders*

**Goals:**

• Promote global recognition and legitimisation of FGIDs

• Advance the scientific understanding of their pathophysiology

• Optimise clinical management for these patients

• Develop and provide educational resources to accomplish these goals
Changes for Rome IV

1. Remove “Functional*” when not needed
   - Removed “Functional” from chapter titles
   - Functional abdominal pain syndrome → Centrally mediated abdominal pain syndrome
   - Functional faecal incontinence → Faecal incontinence
   - Functional GI Disorders → Disorders of Gut-Brain Interaction
   - New definition for Functional GI Disorders

* “Functional” term is retained to distinguish from structural disorders: e.g. functional heartburn, functional diarrhoea
A group of disorders classified by GI symptoms related to any combination of:

- Motility disturbance
- Visceral hypersensitivity
- Altered mucosal and immune function
- Altered gut microbiota
- Altered CNS processing
Changes for Rome IV

1. Remove “functional” when not needed; new definition for Functional GI Disorders (FGIDs)

2. New diagnoses
New Diagnoses in Rome IV

Reflux Hypersensitivity Syndrome
- Heartburn or chest pain with normal endoscopy
- Reflux triggers symptoms despite normal acid exposure

Cannabinoid Hyperemesis Syndrome (CHS)
- Stereotypical vomiting similar to cyclic vomiting syndrome occurring with excessive cannabis use and symptoms
- Relieved after discontinuation

Opioid Induced Constipation (OIC)
- Development of or worsening of constipation symptoms (hard or infrequent stools, straining, incomplete evacuation) when taking opioids

Narcotic Bowel Syndrome (NBS)
- Progressive and paradoxical increase in abdominal pain despite continued or escalating dosages of opioids prescribed to relieve the pain
- Improves with detoxification
Changes for Rome IV

1. Remove “functional” when not needed; new definition for Functional GI Disorders (FGIDs)

2. New diagnoses

3. Threshold changes in diagnostic criteria
Threshold Changes in Diagnostic Criteria

How often did you have discomfort or pain anywhere in your abdomen?

n=1,162

Threshold misclassifies 6.7%.
Changes for Rome IV

1. Remove “functional” when not needed; new definition for Functional GI Disorders (FGIDs)

2. New diagnoses

3. Threshold changes in diagnostic criteria

4. Changes in IBS diagnostic criteria
Rome III Criteria* IBS

Recurrent abdominal pain or discomfort at least 3 days/month in the last 3 months associated with 2 or more:

- Improvement with defecation
- Onset associated with a change in frequency of stool
- Onset associated with a change in form (appearance) of stool

Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

Longstreth G., Gastroenterology, 2006
Rome IV Criteria* IBS

Recurrent abdominal pain or discomfort at least 3 days/month, 1 day/week in the last 3 months associated with 2 or more:

- Improvement with defecation
- Onset associated with a change in frequency of stool
- Onset associated with a change in form (appearance) of stool

Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

Changes for Rome IV

1. Remove “functional” when not needed; new definition for Functional GI Disorders (FGIDs)

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4. Changes in IBS diagnostic criteria

5. Functional bowel disorders exist on a spectrum
Functional Bowel Disorders Exist on a Spectrum

- FC: Functional Constipation
- FDr: Functional diarrhoea
- IBS-C: IBS with predominant constipation
- IBS-M: IBS with mixed bowel habits (D&C)
- IBS-D: IBS with predominant diarrhoea
Changes for Rome IV

1. Remove “functional” when not needed; new definition for Functional GI Disorders (FGIDs)

2. New diagnoses

3. Threshold changes in diagnostic criteria

4. Changes in IBS diagnostic criteria

5. Functional bowel disorders exist on a spectrum

6. IBS subtypes now based on abnormal stools
Rome IV IBS Subtypes: Stool Form

>25% of abnormal BM (types 1, 2, or 6, 7) is the threshold for classification.
Changes for Rome IV

1. Remove “functional” when not needed; new definition for Functional GI Disorders (FGIDs)

2. New diagnoses

3. Threshold changes in diagnostic criteria

4. Changes in IBS diagnostic criteria

5. Functional bowel disorders exist on a spectrum

6. IBS subtypes now based on abnormal stools

7. Eliminated SOD type I and III; new SO criteria
Effect of Sphincterotomy for Suspended SOD Dysfunction Post Cholecystectomy (Type III) on Pain Disability

* p<0.01 adjusted for site and pancreatic sphincter hypertension status

Cotton PB, et al. JAMA 2014; 311:2101
Changes for Rome IV

1. Remove “functional” when not needed; new definition for Functional GI Disorders (FGIDs)

2. New diagnoses

3. Threshold changes in diagnostic criteria

4. Changes in IBS diagnostic criteria

5. Functional bowel disorders exist on a spectrum

6. IBS subtypes now based on abnormal stools

7. Eliminated SOD type I and III; new SO criteria

8. Chronic Nausea Vomiting Syndrome (CNVS) as a single entity
Diagnostic Algorithms – 2\textsuperscript{nd} Edition

Twenty-seven standardised algorithms covering common GI symptoms presentations:

- Up to date evidence-based assessment strategies
- Leads to exclusion of structural disease or makes Rome IV diagnosis
- Adult and paediatric cases
- Each algorithm with a case report, explanations for all decision paths and references

www.romecriteria.org
1. Patient with recurrent abdominal pain associated with defecation and/or disordered bowel habits (constipation, diarrhoea, or a mix)

2. Medical, surgical, psychosocial, dietary, medication history: physical examination including digital rectal exam

3. Alarm features?

4. Patient specific investigations as indicated

5. Abnormality identified?

6. Other disease: treat accordingly

7. Limited screening tests (e.g. CBC, CRP, fecal calprotectin, celiac serologies)

8. Abnormality identified?

9. Irritable Bowel Syndrome (IBS)

10. Evaluation of stool consistency (using Bristol Stool Form Scale)

11. IBS with Constipation (IBS-C)

12. IBS with mixed bowel habits (IBS-M)

13. IBS with diarrhoea (IBS-D)

14. IBS unclassified (IBS-U)
Introducing the MDCP Book – 2\textsuperscript{nd} Edition

Seventy-two cases covering the full spectrum of functional GI diagnoses:

- Greater characterisation of clinical subsets, psychosocial co-morbidities and physiological disturbances
- Rome IV Criteria
- Adult, paediatric and multicultural cases
- Up-to-date treatments
- MDCP slide set for teaching
Multi-Dimensional Clinical Profile

A. Categorical Diagnosis – Symptom-based criteria (may include physiological criteria)

B. Clinical Modifier (e.g. IBS C, D, M, post-infection etiology, FODMAP sensitivity)

C. Impact (mild, moderate, severe)

D. Psychosocial Modifier (DSM 5 diagnosis, abuse history)

E. Physiological Dysfunction and Biomarkers (type and severity)
Functional Dyspepsia (Postprandial Distress Syndrome) – (Moderate)

A 30 year old male accountant sees a gastroenterologist due to upper abdominal bloating and fullness with early satiety occurring after meals almost every day with 4 kg weight loss. Symptoms begin eight months ago after having severe gastroenteritis with vomiting and diarrhoea. Currently there are no bowel symptoms, and the patient reports no heartburn. He reports the symptoms as moderate: they limit his ability to travel and he avoids eating at work, and this has been associated with 4 kg weight loss. He saw a psychiatrist and is taking an SSRI for generalised anxiety disorder. Upper endoscopy with Helicobacter pylori testing and abdominal ultrasound are negative. Proton pump inhibitors are not helpful.

A. Categorical Diagnosis: Functional dyspepsia
B. Clinical Modifier: Post-infection postprandial distress syndrome (PDS)
C. Impact on Daily Activities: Moderate
D. Psychosocial Modifier: Moderate generalised anxiety disorder
E. Physiological Features and Biomarkers: None known
Functional Dyspepsia (Postprandial Distress Syndrome) – (Moderate)

Treatment Options:

- Reassurance

- Buspirone (5HT1 receptor agonist) as a fundus-relaxing drug and to treat anxiety

- Mirtazapine for dyspepsia and anxiety with weight loss

- Continue with psychologist for anxiety management
Rome IV Interactive Clinical Decision Toolkit Rome-LogicNets Collaboration

Captures expert knowledge from Rome to create a novel interactive learning tool
- Rome IV diagnostic algorithms and MDCP provides the basis for expert decisions, yet it is complex and requires multi-dimensional representation
- LogicNets is a visual modelling and decision support engine that optimises the Rome content to produce an online interactive format to accomplish this

Online delivery system
- Clinicians interact directly with decision pathways
- Flexible, customisable – accommodates to user
- Runs on standard browser-compatible devices
- Presentations adaptable for different users (clinicians, trainees, devices)
Feedback and Optimisation

- System processes multiple pathways simultaneously to achieve one or more outcomes
- All diagnosis and treatment steps are recorded
- System then learns and develops probabilities and weights from past entries
- Rome experts review and provide input to weights to modify system’s learning paths

Multiple decision steps and input
Predictive Diagnostics

- System processes multiple pathways simultaneously to achieve one or more outcomes
- All diagnosis and treatment steps are recorded
- System then learns and develops probabilities and weights from past entries
- Rome experts review provide input to weightings to modify system’s learning paths
- Decision pathways improve over time
Diagnostic Questionnaires and Tables
For Investigators and Clinicians

Contains Rome IV adult and paediatric diagnostic tables and questionnaires for clinical and survey research

- Rome IV criteria tables
- Rome IV adult and paediatric diagnostic questionnaires and score sheets
- Psychosocial alarm questions and mental health assessment flowchart
- Chapter on validation of questionnaires
Thank you

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Questions
Multivariate modelling of gut microbial profiles predicts responsiveness to a diet low in FODMAPS

Sean M. P. Bennet
The Sahlgrenska Academy, University of Gothenburg
Irritable Bowel Syndrome (IBS)

Affects 10-20% of adults in the world, with higher prevalence in women than in men.

Functional bowel disorder:
All organs are macroscopically normal yet patients present symptoms characterised by:
• Abdominal pain
• Bloating
• Altered bowel habits

Although not life threatening, it may be painful and debilitating and sufferers can have a severely impacted quality of life.
Irritable Bowel Syndrome (IBS)

Suggested causes and triggers:

- Elevated immune activity
- Altered gut microbiota
- Stress
- Diet
- Gastroenteritis

While currently no known single therapy for IBS, some patients respond to symptom treatment such as:

- Laxatives or Antidiarrhoeals
- Secretagogues
- Pro- or prebiotics
- Psychological treatment / Stress management
- Change in dietary habits
Dietary factors and symptoms in IBS
Dietary intervention may reduce IBS symptoms and impact gut microbiota

Dietary interventions are considered first line treatment for IBS by both patients and treating doctors

Diet effects gut microbiota composition

The degree to which gut microbiota is affected by diet and factors predicting response to dietary intervention are largely unknown
Traditional IBS Diet

• A regular meal plan minimising portion size

• Reduced intake of fat, excessive fibre, caffeine and gas-producing foods such as beans and cabbage

• Eat in a calm manner and to chew thoroughly

• Emphasis on how and when to eat rather than on what food to ingest

Low FODMAP IBS Diet

• Removal of FODMAP foods

• Aims to reduce luminal water retention and luminal distention by rapid gas production through bacterial fermentation

Böhn et.al. Gastroenterology 146(6) August 2015
FODMAPs and symptoms in IBS

Absorption:
- Lactase
- Transit time
- Dose
- Mucosal disease
- Food composition

- Stress
- Anxiety and depression
- Expectation
- Attention/distraction
- Conditioning

GI symptoms
- Visceral hypersensitivity
- Gut inflammation/immune activity
- Barrier defects?
- Other factors

Intestinal distension

H₂O
Gas

Simrén Gastroenterology 2014
Diet and how it affects gut bacteria

- Food not directly used by host becomes food for gut bacteria
- Broken down in several steps by different bacteria until a host absorbable nutrient might be formed
- Species able to metabolise the nutrients in the diet are favoured
- Denotes the types and levels of metabolites produced e.g.
  - Butyrate:  
    - or too much methane

SCFA
Host tissue
Reduced FODMAP intake lowers abundance of potentially beneficial bacteria e.g. Bifidobacteria

Halmos et.al. Gut 2015

Staudacher et.al. J Nutr 2012
Alteration of the microbiota

• May be associated with a decrease in beneficial species

• However can also be a shift from a “normal/healthy biota” (normobiosis)

• A dysbiotic microbiota may be less diverse and not sufficiently fulfill important roles that a diverse microbiota of normobiosis does
Low FODMAP and traditional IBD dietary advice both reduce IBS symptoms

- 75 IBS patients followed either a low FODMAP or traditional IBS diet for 4 weeks
- The number of patients classified as “responders”, i.e. reporting a significant reduction in IBS symptoms, was similar for both diets

Unknown impact and involvement of gut microbiota
Investigation of faecal microbiota composition before and after a low FODMAP diet and traditional IBS dietary advice

Hypothesis

• Gut bacteria profiles are altered through dietary intervention

• IBS patient responsiveness to dietary intervention may be linked to gut bacteria composition before intervention starts

Aim

• To determine if dietary interventions affect gut bacteria composition

• To determine if responders to intervention can be discriminated from non-responders based on gut bacteria composition before intervention
Study design

10 Day Screening period

28 Day intervention period

Traditional Diet
n = 30

Low FODMAP Diet
n = 31

IBS symptoms recorded

Visit 2
(Day 0)
IBS symptoms recorded

Visit 3
(Day 29)
IBS symptoms recorded

Microbial Analysis

<table>
<thead>
<tr>
<th>Diet</th>
<th>IBS-C</th>
<th>IBS-D</th>
<th>IBS-nonCnonD</th>
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<tbody>
<tr>
<td>Traditional</td>
<td>9</td>
<td>5</td>
<td>16</td>
</tr>
<tr>
<td>Low FODMAP</td>
<td>8</td>
<td>11</td>
<td>12</td>
</tr>
</tbody>
</table>
Faecal microbial profiling performed using the GA-MAP™ 16s rRNA Dysbiosis Test

- 54 DNA probes assessing the abundance of ≥300 bacteria demonstrated to be associated with disease or gut disorders

- Output:
  1. Microbial profile based on 54 probes
  2. Dysbiosis Index Value (DI), how much the microbial profile deviates from a reference ‘healthy’ microbial composition

Casén C et al.. Aliment Pharmacol Ther. 2015;42(1):71-83.
Patients on a traditional IBS diet had similar faecal bacterial profiles before intervention.

Responders could not be discriminated from non-responders before intervention based on bacterial profiles.

$R^2 = 0.5$

$Q^2 = 0.3$

$R^2$ = How well the model mathematically reproduces the data

$Q^2$ = Predictability power of the model
Patients on a traditional IBS diet had similar faecal bacterial profiles after intervention.

Orthogonal component

Responders could not be discriminated from non-responders after intervention based on bacterial profiles.

\[ R^2 = 0.5 \]
\[ Q^2 = 0.3 \]

- \( R^2 \): How well the model mathematically reproduces the data
- \( Q^2 \): Predictability power of the model

Threshold for model robustness

Traditional Diet
Patients on a low FODMAP IBS diet had different faecal bacterial profiles before intervention.

Responders could be discriminated from non-responders before intervention based on bacterial profiles.
Patients on a low FODMAP IBS diet had different faecal bacterial profiles after intervention. Responders could be discriminated from non-responders after intervention based on bacterial profiles. 

Low FODMAP Diet

- $R^2 = 0.5$
- $Q^2 = 0.3$

$R^2$ = How well the model mathematically reproduces the data

$Q^2$ = Predictability power of the model

Responder vs Non-responder

Responders could be discriminated from non-responders after intervention based on bacterial profiles.
Non-responders to a low FODMAP diet more dysbiotic than responders

Before Intervention

A

B

After Intervention

p=0.007

p=0.03

Dysbiosis Index

Before Intervention

A

Non-Responders

Responders

After Intervention

B

Non-Responders

Responders

Patients on a traditional IBS diet had similar dysbiosis irrespective of responsiveness.
Dysbiosis improved after a traditional diet but worsened after a low FODMAP diet

### A. Traditional IBS Diet
- **Improved Di**: 33%
- **Unchanged Di**: 47%
- **Worsened Di**: 20%

### B. low FODMAP Diet
- **Improved Di**: 13%
- **Unchanged Di**: 45%
- **Worsened Di**: 42%

**Change in dysbiosis index**
(Before to after intervention)
Significant reduction in Bifidobacterium after a low FODMAP diet

The traditional IBS diet intervention had no effect on abundance of Bifidobacterium
Summary

• Low FODMAP diet, but not traditional IBS diet influence faecal bacterial composition

• Low FODMAP diet, but not traditional IBS diet responders could be discriminated from non-responders before intervention based on faecal bacterial profiles

• Severity of dysbiosis was generally increased in patients after a low FODMAP diet but not after a traditional IBS diet

• Non-responders to a low FODMAP diet had more severe dysbiosis than responders at baseline
Conclusion

• Faecal bacteria profiles predict IBS patient responsiveness to a low FODMAP diet

• The ability of faecal bacteria composition to predict response to a low FODMAP diet in IBS may help in selection of which patients to give this dietary advice
Acknowledgements

Supervisors: Lena Öhman and Magnus Simrén

Colleagues: Lena Böhn, Stine Störsrud, Therese Liljebo, Lena Collin, Perjohan Lindfors, Hans Törnblom
## Correlation of bacteria and dietary components

<table>
<thead>
<tr>
<th>Bacterial target of labelling probe</th>
<th>Dietary Parameter (g)</th>
<th>$p$-value*</th>
<th>$p$-value†</th>
<th>q-value‡</th>
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</thead>
<tbody>
<tr>
<td><strong>Tradition IBS diet</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus</em></td>
<td>Protein</td>
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<td>0.0009</td>
<td>0.001</td>
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<td>Alcohol</td>
<td>-0.463</td>
<td>0.0002</td>
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<tr>
<td>Firmicutes (<em>Bacilli and Clostridia</em>)</td>
<td>Polyols</td>
<td>0.441</td>
<td>0.0005</td>
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<td><strong>Low-FODMAP diet</strong></td>
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<tr>
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<td>0.0009</td>
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<td>Actinobacteria</td>
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<td>0.390</td>
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</table>

*Spearman's rank correlation coefficient
†Mann Whitney U test. Data shown as median (25%-75%)
‡Correction for multiple comparisons, using Classical one-stage method
Low FODMAP diet

### Some foods which contain FODMAPS to eliminate

**Fruit**
- Apples
- Apricots
- Cherries
- Pears
- Watermelon
- Dried fruit

**Vegetables**
- Asparagus
- Broccoli
- Cabbage
- Eggplant
- Garlic
- Mushrooms
- Onions

**Cereals / Grains**
- Wheat
- Rye
- Pasta
- Bread
- Cookies

**Other**
- Sweeteners: sorbitol, mannitol, isomalt
- Fructose, corn syrup, honey

**Milk Products**
- Cow’s milk
- Custard
- Ice cream
- Yogurt
- Soft cheeses

**Beans / Legumes**
- Chickpeas
- Kidney beans
- Lentils
- Soybeans

### Some foods which are suitable for a low FODMAP diet

**Fruit**
- Bananas
- Blueberries
- Grapefruit
- Lemons
- Raspberries

**Vegetables**
- Carrots
- Celery
- Green beans
- Potatoes
- Pumpkin
- Zucchini

**Cereals / Grains**
- Gluten free bread or cereal
- Rice
- Oats
- Polenta
- Tapioca

**Other**
- Tofu
- Sugar
- Maple syrup
- Molasses

**Milk Products**
- Lactose-free milk and yogurt
- Hard cheeses

Images courtesy of www.wikipedia.org
Thank you
Questions