Improving Primary Care Management of IBS-D through Early Diagnosis and Personalized Treatment

Presented by:
Lucinda Harris, MD, MS

Approved for 1.0 Prescribed CME

Saturday, August 4, 2018
8:00—9:00am
Faculty Affiliation

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Learning Objectives

- Apply an approach to the diagnosis of irritable bowel syndrome with diarrhea (IBS-D) that is consistent with current evidence-based guidelines
- Identify strategies for encouraging effective provider-patient communication to improve assessment of disease burden in patients with IBS-D
- Summarize current evidence regarding the efficacy and safety of available options for the treatment of IBS-D

Overview of IBS

- Most frequently diagnosed functional GI disorder in primary and secondary care practices
- Affects ~10%-20% of adults in Western countries; estimated global prevalence of 11%
- Characterized by recurrent abdominal pain accompanied by altered bowel function in the absence of structural or biochemical abnormalities
- Subtypes include IBS with constipation (IBS-C), IBS-D, mixed IBS (IBS-M), and un-subtyped IBS depending on the predominant stool pattern
- Associated with high medical costs, frequent doctor visits, missed workdays, and an overall detrimental impact on HRQOL

Healthcare Provider Understanding of the Burden of IBS

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>18%</td>
<td>Not at all</td>
</tr>
<tr>
<td>29%</td>
<td>Not very well</td>
</tr>
<tr>
<td>31%</td>
<td>Somewhat well</td>
</tr>
<tr>
<td>17%</td>
<td>Very well</td>
</tr>
<tr>
<td>18%</td>
<td>Extremely well</td>
</tr>
</tbody>
</table>

Pathogenesis of IBS

EXTRINSIC FACTORS

Psychological stress, abuse (sexual, physical), smoking, diet
Infection, dysbiosis


5. IBS prevalence. Recent advances in the diagnosis and management of IBS. J Gastroenterol. Hepatol. 2009;24(11):2107-12
6. IBS prevalence. Recent advances in the diagnosis and management of IBS. J Gastroenterol. Hepatol. 2009;24(11):2107-12
Diagnosis of IBS

**Rome IV Criteria**

1. Symptom onset 26 months prior to diagnosis
2. Recurrent abdominal pain, on average, ≥1 day/week in the last 3 months with ≥2 of the following:
   - Related to defecation
   - Associated with a change in stool frequency
   - Associated with a change in stool form (appearance)

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Comorbidities Associated with IBS

- 91% of patients with IBS reported ≥1 comorbidity
- Average number reported was 5 (1 mental, 4 physical)
- Anxiety, depression, back pain, agoraphobia, tension headache, insomnia were associated with greater illness and symptom burden

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Screening and Diagnosis

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Rome IV Criteria for Frequency of Stool

Rome IV classified by stool forms ONLY during days of abnormal BMs rather than total # of BMs

- Subtype criteria are now
  - IBS-C - >25% of BMs BSF 1-2 and <25% BSF 6-7
  - IBS-D - >25% of BMs BSF 6-7 and <25% BSF 1-2
  - IBS-M - >25% of BMs BSF 1-2 and >25% BSF 6-7
  - IBS-U - Pts meet diagnostic criteria for IBS but cannot be accurately categorized in any of above subtypes
Bristol Stool Form Scale

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
<th>Image</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Separate hard lumps, like nuts</td>
<td>![Image 1]</td>
</tr>
<tr>
<td>2</td>
<td>Sausage-shaped but lumpy</td>
<td>![Image 2]</td>
</tr>
<tr>
<td>3</td>
<td>Like a sausage or snake but with cracks on its surface</td>
<td>![Image 3]</td>
</tr>
<tr>
<td>4</td>
<td>Like a sausage or snake, smooth and soft</td>
<td>![Image 4]</td>
</tr>
<tr>
<td>5</td>
<td>Soft blobs with clear-cut edges</td>
<td>![Image 5]</td>
</tr>
<tr>
<td>6</td>
<td>Fluffy pieces with ragged edges, a mushy stool</td>
<td>![Image 6]</td>
</tr>
<tr>
<td>7</td>
<td>Watery, no solid pieces</td>
<td>![Image 7]</td>
</tr>
</tbody>
</table>

Available at: https://www.bristol-stool-form-scale.net/十大便型.jpg

Case Study #1: 35-year-old Female

- **Clinical presentation and medical history**
  - 5-year history of recurrent abdominal pain and diarrhea
  - 3-4 loose bowel movements each day
  - Abdominal pain
    - Associated with bloating and gas
    - Exacerbated by eating
    - Relieved with defecation
  - Episodes are more frequent during times of stress
  - No specific triggers identified
  - No recent travel outside the US
  - No reported weight loss
  - No family history of GI disorders or malignancies

Case Study #1 (cont’d)

- **Psychosocial effects and social history**
  - Sleep quality is impaired
  - GI symptoms are having a negative impact on the patient’s ability to concentrate at work
  - Patient reports anxiety about engaging in her usual social activities

Case Study Discussion

- Individual symptoms have limited accuracy
- Alarm features are crucial for guidance
- Disease impact on patient ability to function and QOL are important considerations
- Recommended diagnostic tests

Rome IV Recommendations for Diagnostic Testing

- CBC, CRP, and fecal calprotectin to exclude IBD
- Routine thyroid testing if clinically warranted
- Celiac tests
- Stool analysis (bacteria, parasites, and ova)
- Breath testing to identify carbohydrate malabsorption
- Colonoscopy
  - ≥50 years of age* in the absence of warning signs
  - History of colorectal cancer
  - Persistent diarrhea that has failed empiric therapy
  - Bile acid malabsorption testing

Red Flags for Organic Conditions

- Fever
- Unexplained weight loss
- Rectal bleeding or melena
- Nocturnal diarrhea
- Unexplained iron-deficiency anemia
- Symptom onset after 50 years of age
- Severe or progressively worsening symptoms
- Family history of organic GI diseases (eg, colon cancer, celiac disease, or IBD)

Comparative Positivity Rates for Anti-CdtB and Anti-vinculin across IBS Subtypes

*Age 45 years of age in African Americans.


CdtB, cytolethal distending toxin B; Anti-vinculin: Anti-vinculin+; Anti-CdtB+ or Anti-vinculin+.
Clinical Applications: Multidimensional Clinical Profile Categories (MDCP)

- MDCP helps characterize IBS illness state to apply to Rx plan.

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<th>Examples</th>
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<td>A. Diagnosis based on Rome IV Criteria</td>
<td>Bowel habit predominance (D, C, M or U), Post-infectious IBS, gluten sensitivity</td>
</tr>
<tr>
<td>B. Clinical Modifiers</td>
<td>Mild, moderate or severe</td>
</tr>
<tr>
<td>D. Psychosocial Modifier of comorbidities</td>
<td>Can be categorical, e.g. DSM Axis I, pt reported (e.g. abuse) or dimensional (HADS, psychosocial red flags)</td>
</tr>
<tr>
<td>E. Physiologic modifiers, biomarkers of clinical significance that enhance understanding of diagnosis.</td>
<td>Motility studies, antibodies, biochemical</td>
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Goals of Treatment

- Improve individual symptoms
- Ameliorate global symptoms
- Prevent complications
- Reduce impact on the individual and society

Case Study #2: 30-year-old Male

- Medical history
  - 2-year history of abdominal pain and diarrhea
  - Intermittent episodes of lower abdominal cramping and bloating associated with 4-5 loose bowel movements occurring 2-3 days per week
  - Abdominal pain occurs shortly after meals or with increased stress, diminishes following a bowel movement

- Social history
  - Is an investigative journalist at a large metropolitan newspaper
  - Eating habits are unpredictable due to erratic schedule and frequent deadlines
  - Symptoms often interfere with the demands of his job

Case Study Discussion

- Inadequate symptom control/response to conventional therapies is common
- Dietary strategies
- Newer pharmacologic management strategies
- Potential role of combining therapies
- Consideration of adverse effects
- Psychological interventions

Rome IV Treatment of IBS-D Algorithm

Treatment of IBS-D Pharmacologic Options
**Triple-Coated Peppermint Oil for IBS**

- RCT of triple-coated peppermint oil microspheres in IBS-M or IBS-D (N=72)
  - Randomized to peppermint oil 180 mg TID or placebo for 4 weeks
  - Primary analysis based on TSS
- Peppermint oil improved TSS (P<.02) and frequency and intensity of individual IBS symptoms over 4 weeks
- Most frequent AEs with peppermint oil and placebo were dyspepsia and URT infection (2.9% vs 0% for each)

**Guidelines for IBS-D Treatment**

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<th>Medication</th>
<th>Society</th>
<th>Recommendation</th>
<th>Quality of Evidence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loperamide</td>
<td>AGA</td>
<td>Strategic</td>
<td>Very-low</td>
<td>Unit cost, wide availability, minimal adverse effects</td>
</tr>
<tr>
<td>Rifaximin</td>
<td>AGA</td>
<td>Conditional</td>
<td>Moderate</td>
<td>Minimal side effects; expensive</td>
</tr>
<tr>
<td>Alosetron</td>
<td>AGA</td>
<td>Condition</td>
<td>Moderate</td>
<td>Quality of evidence is greater for abdominal pain; only approved for women with ischemic colitis</td>
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<tr>
<td>Antispasmodics</td>
<td>AGA</td>
<td>Conditional</td>
<td>Low</td>
<td>Low cost, wide availability, minimal adverse effects</td>
</tr>
<tr>
<td>ACG</td>
<td>AGA</td>
<td>Weak</td>
<td>Moderate*</td>
<td></td>
</tr>
<tr>
<td>Tricycics</td>
<td>AGA</td>
<td>Conditional</td>
<td>Low</td>
<td>Used with caution in patients with prolonged QT</td>
</tr>
<tr>
<td>SSRIIs</td>
<td>AGA</td>
<td>Conditional</td>
<td>High</td>
<td>No improvement in abdominal pain; adverse effects is minimal</td>
</tr>
<tr>
<td>ACG</td>
<td>AGA</td>
<td>Weak</td>
<td>High</td>
<td>Can be expensive</td>
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**Impact of Alosetron Treatment in Women with Severe IBS-D**

- Symptom Reduction at Day 29
  - Abdominal Pain or Discomfort
  - Abdominal Bloating or Distension
  - Pain at Evacuation

**Newer Agents for the Treatment of IBS-D**

- **Alosetron**
  - Inhibits GI motility via antagonism of 5-HT3 receptors of the enteric nervous system and possibly within the central nervous system
- **Eluxadoline**
  - Mu and kappa opioid receptor agonist and delta opioid receptor antagonist
- **Rifaximin**
  - Is a broad antibiotic against GI aerobic and anaerobic Gram-positive and Gram-negative bacteria (may allow resetting of the microbiota)
  - Alters the inflammatory environment and bacterial end products in patients with various GI disorders

**Adverse Events of Alosetron**

- **Most common AEs (%)**
  - Constipation: 5, 9, 16, 19
  - Abdominal pain: 3, 5, 6, 7
  - Nausea: 6, 5, 3, 6
  - Sinusitis: 6, 3, 3, 6
  - Headaches: 2, 5, 5, 2

- **AEs for symptoms of potential ischemic colitis**
  - Any event: Placebo (n=176) vs Alosetron (n=175)
  - 0.5 mg OD: 1%, 1%, 1%, 1%
  - 1 mg OD: 2%, 2%, 2%, 2%
  - 1 mg BID: 3%, 3%, 3%, 3%

**Alosetron: REMs Program**

- Infrequent, but serious, GI adverse reactions (eg, ischemic colitis, serious complications of constipation) reported: some have resulted in hospitalization and, rarely, blood transfusion, surgery, or death
- Prescribing physicians must be enrolled in Prescribing Program for Lotronex
- Indicated only for women with severe IBS-D who have not responded adequately to conventional therapy
- Discontinue immediately in patients who develop constipation or symptoms of ischemic colitis; do not resume in those who develop ischemic colitis

**Eluxadoline Treatment Results in Sustained Reduction of IBS-D Symptoms over 6 Months**

- Represents composite primary efficacy endpoint.
- *P<.05, **P<.01, ***P<.001

**Eluxadoline treatment resulted in more patients reporting a ≥30% reduction in abdominal pain score and a stool-consistency score <5 on ≥50% of the days**
Eluxadoline in the Clinic

Dosage
- 100 mg BID taken with food
- 75 mg BID with food in patients who
  - Do not have a gallbladder
  - Are unable to tolerate 100 mg BID
  - Are receiving concomitant OATP1B1 inhibitors
  - Have mild or moderate hepatic impairment

Contraindications
- Bile duct obstruction
- Sphincter of Oddi disease or dysfunction
- Pancreatitis
- Severe liver impairment (Child-Pugh Class C)
- Severe constipation
- Patients who consume >3 alcoholic drinks per day

Eluxadoline Adverse Events

Most Common Adverse Events in Phase 3 Trials (>4% in either treatment arm and > placebo)

<table>
<thead>
<tr>
<th>Event</th>
<th>Eluxadoline 75 mg</th>
<th>Rifaximin 550 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>3 (3.7)</td>
<td>1 (1.2)</td>
<td>2 (2.6)</td>
</tr>
<tr>
<td>Drug-related AE</td>
<td>7 (8.1)</td>
<td>3 (3.7)</td>
<td>2 (2.6)</td>
</tr>
<tr>
<td>Serious AE</td>
<td>27 (3.3)</td>
<td>1 (1.2)</td>
<td>4 (1.3)</td>
</tr>
</tbody>
</table>

Rifaximin Treatment Is Associated with Sustained Reduction of IBS Symptoms over 12 Weeks

Safety and Tolerability of Rifaximin

<table>
<thead>
<tr>
<th>AE, n (%)</th>
<th>Open-Label Population</th>
<th>Double-Blind Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifaximin 550 mg TID (n=328)</td>
<td>822 (31.9)</td>
<td>140 (42.7)</td>
</tr>
<tr>
<td>Rifaximin 550 mg TID (n=308)</td>
<td>822 (31.9)</td>
<td>140 (45.5)</td>
</tr>
<tr>
<td>Placebo (n=308)</td>
<td>822 (31.9)</td>
<td>140 (45.5)</td>
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</table>

Common Adverse Effects Observed with Rifaximin Treatment

Dietary Considerations in IBS

- FODMAPs are an important trigger of meal-related symptoms in IBS.
- Low FODMAP diet found to improve overall symptom scores compared with typical diet in IBS patients.
- Gluten-free diet found to be beneficial in some patients with IBS.
- Wheat contains fructans and other proteins that may also cause symptoms in IBS patients.
- Food antigens found to cause changes in the intestinal mucosa of IBS patients that are associated with patient responses to exclusion diets.

*Infections: aspiration pneumonitis, increased interstitial spaces, and increased interstitial lymphocytes demonstrated via confocal laser endomicroscopy in 23 of 36 patients with IBS.

FODMAP Diet Reduces Functional GI Symptoms

- **Effects of Diet on Functional GI Symptoms in Controlled, Crossover Study (N=30)**

  - Typical Australian diet
  - Low FODMAP diet

<table>
<thead>
<tr>
<th>Study Day</th>
<th>Placebo</th>
<th>Bran 10 g</th>
<th>Psyllium 10 g</th>
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<tbody>
<tr>
<td>0</td>
<td>68</td>
<td>69</td>
<td>67</td>
</tr>
<tr>
<td>5</td>
<td>58</td>
<td>60</td>
<td>58</td>
</tr>
<tr>
<td>10</td>
<td>47</td>
<td>50</td>
<td>47</td>
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<tr>
<td>15</td>
<td>38</td>
<td>41</td>
<td>38</td>
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<tr>
<td>20</td>
<td>30</td>
<td>33</td>
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</tr>
<tr>
<td>25</td>
<td>22</td>
<td>25</td>
<td>22</td>
</tr>
<tr>
<td>30</td>
<td>14</td>
<td>16</td>
<td>14</td>
</tr>
</tbody>
</table>

  *P<.05 vs placebo.

Soluble vs Insoluble Fiber for IBS

- **Proportion of Patients with Adequate Relief of Symptoms**

<table>
<thead>
<tr>
<th>Month</th>
<th>Placebo (n=93)</th>
<th>Bran 10 g (n=97)</th>
<th>Psyllium 10 g (n=85)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>12%</td>
<td>13%</td>
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</tr>
<tr>
<td>2</td>
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<td>12%</td>
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</tr>
<tr>
<td>3</td>
<td>10%</td>
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  *P<.05 vs placebo.

Benefit of a Gluten-Free Diet in Patients with IBS-D

- **A dietitian-led GFD provided sustained benefit to patients with IBS-D. The symptoms that improved differed in magnitude according to HLA-DQ status.**

Impact of Psychological Intervention on IBS Symptoms

<table>
<thead>
<tr>
<th>Treatment Modality</th>
<th>Studies (n)</th>
<th>Psychological Therapies/Controls (n)</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total psychological therapies</td>
<td>12/32/1102</td>
<td>0.68 (0.61-0.76)</td>
<td>&lt; .00001</td>
<td></td>
</tr>
<tr>
<td>CBT</td>
<td>9</td>
<td>349/261</td>
<td>0.60 (0.64-0.83)</td>
<td>.002</td>
</tr>
<tr>
<td>CBT via internet</td>
<td>2</td>
<td>75/71</td>
<td>0.75 (0.66-1.07)</td>
<td>NS</td>
</tr>
<tr>
<td>Self-administered/minimal contact CBT</td>
<td>3</td>
<td>75/71</td>
<td>0.53 (0.37-0.86)</td>
<td>NS</td>
</tr>
<tr>
<td>Relaxation training or therapy</td>
<td>6</td>
<td>133/122</td>
<td>0.77 (0.57-1.04)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypnotherapy</td>
<td>5</td>
<td>142/137</td>
<td>0.74 (0.63-0.87)</td>
<td>&lt; .0002</td>
</tr>
<tr>
<td>Multicomponent psychotherapy</td>
<td>5</td>
<td>168/167</td>
<td>0.72 (0.62-0.83)</td>
<td>&lt; .00001</td>
</tr>
<tr>
<td>Multicomponent psychotherapy via telephone</td>
<td>1</td>
<td>44/42</td>
<td>0.76 (0.64-0.92)</td>
<td>.008</td>
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<tr>
<td>Group psychotherapy</td>
<td>2</td>
<td>138/135</td>
<td>0.60 (0.30-1.09)</td>
<td>NS</td>
</tr>
<tr>
<td>Stress management</td>
<td>2</td>
<td>55/59</td>
<td>0.65 (0.10-2.08)</td>
<td>NS</td>
</tr>
<tr>
<td>Mindfulness mediation</td>
<td>1</td>
<td>36/39</td>
<td>0.57 (0.32-1.01)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*P<.05 vs placebo.

Considerations for Long-term Management

- **Changes in Psychological Interventions**
  - CBT, cognitive behavioral therapy; CI, confidence interval; NS, not significant.

- **Effects of Diet on Functional GI Symptoms in Controlled, Crossover Study (N=30)**

  - Typical Australian diet
  - Low FODMAP diet

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<td>0.60 (0.30-1.09)</td>
<td>NS</td>
</tr>
<tr>
<td>Stress management</td>
<td>2</td>
<td>55/59</td>
<td>0.65 (0.10-2.08)</td>
<td>NS</td>
</tr>
<tr>
<td>Mindfulness mediation</td>
<td>1</td>
<td>36/39</td>
<td>0.57 (0.32-1.01)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*P<.05 vs placebo.

- **Changes in Psychological Interventions**
  - CBT, cognitive behavioral therapy; CI, confidence interval; NS, not significant.
Improving Physician-Patient Communication: Encouraging Patients to Speak Up

**Early**
Talk to healthcare providers about recurring abdominal pain and bowel symptoms rather than suffering in silence or taking advice from non-healthcare professionals.

**Completely**
Instead of just saying “I have constipation” or “I have diarrhea,” tell healthcare providers about the full extent of symptoms, how they impact life, and what approaches have been tried to manage them.

**Often**
Inform healthcare providers if symptoms return despite treatment efforts so they can assess alternatives.

Additional IBS Resources
- The ROME Foundation - http://theromefoundation.org/
- Irritable Bowel Syndrome Association - http://www.ibsgroup.org/ibsassociation.org/
- IBS Page (list of IBS websites) - http://ibspage.com/

Questions & Answers

Thank You!

Eluxadoline Improves Symptoms of IBS-D Independent of Prior Loperamide Use

**Summary**
- IBS-D is a commonly occurring functional bowel disorder that has a pervasive negative impact on the physical, social, and economic well-being of affected individuals.
- Diagnosis is based upon a thorough clinical history and physical examination, in conjunction with application of the Rome IV criteria.
- Treatment options include several pharmacologic and nonpharmacologic strategies that have shown efficacy at reducing IBS-D symptoms and improving QOL.
- Long-term management should be highly individualized and include education and support to promote disease understanding, ensure adherence, and guide therapeutic expectations.
Adverse Events of Treatment with Eluxadoline

SAs, serious adverse events.

Typical Features of IBS

- Loose/frequent stools
- Constipation
- Bloating
- Abdominal cramping, discomfort, or pain
- Symptoms:
  - Brought on by food intake/specific food sensitivities
  - Dynamic over time (change in pain location, change in stool pattern)

Biomarkers for the Diagnosis of IBS-D

<table>
<thead>
<tr>
<th>Type</th>
<th>Biomarker</th>
<th>Diagnostic Utility</th>
<th>Availability</th>
<th>Cost-effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum</td>
<td>Inflammatory (interleukins, cytokines)</td>
<td>Low</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Enteroendocrine (serotonin, chromogranin)</td>
<td>Low</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Fecal</td>
<td>Fecal bile acids</td>
<td>High</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Soluble mediators (proteases, chromogranin, cytokinase)</td>
<td>Low</td>
<td>Moderate</td>
<td>Low</td>
</tr>
<tr>
<td>Microbiome*</td>
<td></td>
<td>Moderate</td>
<td>Moderate</td>
<td>Low</td>
</tr>
<tr>
<td>GI Tract</td>
<td>Colonic transit*</td>
<td>High</td>
<td>Moderate</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Neural hypersensitivity*</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal biomarkers (mast cells, B &amp; T cells, enteroendocrine - mRNA*)</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Neurological &amp; physiological</td>
<td>Pain imaging*</td>
<td>Moderate</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Psychological markers*</td>
<td>Moderate</td>
<td>High</td>
<td>Low</td>
</tr>
</tbody>
</table>

*For availability: high = widely available; moderate = available only in specialized labs/center; low = only available in referral labs/center. * Application in IBS-C as well; IBS (pain).

The Rome Multi-dimensional Clinical Profile Diagnostic (MDCP) Classification

- Categorical diagnosis
  - Standard symptom-based Rome III (or IV) diagnostic criteria
- Clinical modifiers
  - Subcategories categorical diagnosis in ways that potentially affect treatment
- Impact on daily activities
  - Quantifies overall impact of patient illness on their behaviors and daily functioning to guide treatment
- Psychosocial modifiers
  - Identifies psychological and psychosocial modifiers and comorbidities that influence patient experience of their illness and affects treatment options
- Physiological modifiers of function and biomarkers
  - Physiologic parameters that may enhance understanding of the diagnosis or affect treatment
