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SPECIAL REPORTS

Functional Bowel Disorders: A Roadmap to Guide the Next Generation of Research

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In June 2016, the National Institutes of Health hosted a workshop on functional bowel disorders (FBDs), particularly irritable bowel syndrome, with the objective of elucidating gaps in current knowledge and recommending strategies to address these gaps. The workshop aimed to provide a roadmap to help strategically guide research efforts during the next decade. Attendees were a diverse group of internationally recognized leaders in basic and clinical FBD research. This document summarizes the results of their deliberations, including the following general conclusions and recommendations. First, the high prevalence, economic burden, and impact on quality of life associated with FBDs necessitate an urgent need for improved understanding of FBDs. Second, preclinical discoveries are at a point that they can be realistically translated into novel diagnostic tests and treatments. Third, FBDs are broadly accepted as bidirectional disorders of the brain−gut axis, differentially affecting individuals throughout life. Research must integrate each component of the brain−gut axis and the influence of biological sex, early-life stressors, and genetic and epigenetic factors in individual patients. Fourth, research priorities to improve diagnostic and management paradigms include enhancement of the provider−patient relationship, longitudinal studies to identify risk and protective factors of FBDs, identification of biomarkers and endophenotypes in symptom severity and treatment response, and incorporation of emerging "-omics" discoveries. These paradigms can be applied by well-trained clinicians who are familiar with multimodal treatments. Fifth, essential components of a successful program will include the generation of a large, validated, broadly accessible database that is rigorously phenotyped; a parallel, linkable biorepository; dedicated resources to support peer-reviewed, hypothesis-driven research; access to dedicated bioinformatics expertise; and oversight by funding agencies to review priorities, progress, and potential synergies with relevant stakeholders.

Keywords: IBS; Brain−Gut Axis; Intestinal Barrier Dysfunction; Microbiome.

In 2015, the American Gastroenterological Association's James W. Freston Single Topic Conference focused on advances in the understanding and management of irritable bowel syndrome (IBS). That conference highlighted the need for additional resources and strategies to address gaps in the current understanding of the pathophysiology and management of IBS and, more broadly, of functional bowel disorders (FBDs).

A subsequent 2016 meeting, Functional Bowel Disorders Workshop: Future Research Directions in Pathophysiology, Diagnosis and Treatment, was sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases and aimed to elucidate current gaps in knowledge and recommend strategies to address these gaps. The workshop covered a broad range of topics, including prevalence of FBDs and economic burden; pathophysiology and pathogenesis of FBDs; the role of animal models; neuromuscular dysfunction in FBDs (neurons, smooth muscle, glia, interstitial cells of Cajal) and the microbiome; brain−gut pathways in models of IBS and the role of primary afferent, efferent, and spinal components of the axis; evidence of IBS-related dysfunctional circuits in the human brain; genetic and epigenetic mechanisms and environmental factors; the emerging role of dietary triggers in IBS; current and emerging strategies to manage FBDs; and application of next-generation -omics technologies to diagnose and treat FBDs with precision medicine. The presentations focused primarily on IBS because it is the one of the most common diagnoses in gastroenterology and primary care medicine in the outpatient setting. In addition, clinical symptoms of IBS overlap with those of other disorders often affecting patients seen for chronic pain concerns. Each author was

Abbreviations used in this paper: CNS, central nervous system; ENS, enteric nervous system; FBD, functional bowel disorder; FODMAPs, fermentable, oligo-, di-, monosaccharides and polyols; GI, gastrointestinal; IBS, irritable bowel syndrome; IPAN, intrinsic primary afferent neuron.

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assigned a portion of this manuscript. After the initial draft was written, all authors participated in subsequent revisions. Our consensus viewpoint is that the document accurately represents a synthesis of the presentations at the workshop, including gaps in the current understanding and strategies to address these gaps.

Prevalence of Functional Bowel Disorders and Economic Burden

The definition of FBDs recently was updated to include disorders that often involve brain–gut interactions and result in any of the following gastrointestinal (GI) symptoms: motility disturbance, visceral hypersensitivity, altered mucosal and immune function, altered gut microbiota, and altered central nervous system (CNS) processing.[1] The most common conditions in this group (and in gastroenterology in general) include IBS, functional dyspepsia, idiopathic gastroparesis, functional constipation, functional abdominal pain, and disorders of anorectal function; notably, these conditions can arise at any point in life. In pediatric populations, the prevalence of FBDs is increasing, and FBDs are considered a leading cause of school absenteeism.[2]

During the past 3 decades, investigators have noted that FBDs increasingly are recognized by concomitant morphologic and physiologic abnormalities. The diagnostic criteria for functional GI disorders are being standardized by the Rome Foundation; by identifying clustering symptoms, clinicians can better differentiate among these disorders, and more reliable data can be collected on the prevalence of FBDs.[1] In addition, improved population-based data systems are providing a more accurate representation of the true prevalence of FBDs in the United States.

GI disorders are common and costly. Recently, investigators have reported that at least 20% of the US population has chronic symptoms that can be attributable to GI disorders, with common clinical tests showing no evidence of organic causes.[3,4] Everhart and Ruhl[5] determined that GI diseases affect approximately 60 to 70 million US residents annually. In 2004, an estimated 4.6 million hospitalizations, 72 million ambulatory care visits, and 236,000 deaths were attributable to GI diseases.[5] Forty percent of these GI conditions have been attributed to FBDs.[5–9] The direct and indirect costs were estimated to be $142 billion per year.[5] In addition to the economic burden, FBDs affect the individual's health-related quality of life, work productivity, and activities of daily living. When compared with population norms, individuals with FBDs have worse quality of life and markedly more work and activity impairments.[6,8,10]

Research discoveries in the area of brain–gut interactions have improved the understanding of the associated pathophysiologic features relevant to specific FBDs. Furthermore, the findings reported at this workshop indicate that significant advances in the understanding of FBD pathophysiology can be used to identify opportunities for developing much-needed diagnostic and treatment strategies.

Pathophysiology and Pathogenesis of Functional Bowel Disorders

Excellent reviews have been published recently that describe the current understanding of the pathophysiology and pathogenesis of FBDs, particularly IBS.[11–13] The purpose of this article is to focus on identifying gaps in our understanding of the pathophysiology and treatment of FBDs, such as IBS, and to suggest strategies to address these gaps.

Role of Animal Models

The development of relevant animal models to study FBDs has been problematic because current diagnostic criteria for FBDs in humans are based on symptoms, which can be difficult to reproduce and interpret in animals. Among the challenges confronting the development of animal models specifically for IBS is the complex clinical phenotype that overlaps with many other conditions (eg, anxiety, depression, fibromyalgia, post-traumatic stress disorder, painful bladder syndrome, chronic pelvic pain, chronic fatigue syndrome). The multifactorial nature of IBS and the complicated interactions among biologic and psychosocial variables are such that no current animal model is ideally suited to investigate the causal mechanisms.[14] However, we note that these limitations are not unique to FBDs; they apply equally to the study of many neurologic and metabolic disorders.

Despite the drawbacks of animal models, preclinical research remains an essential tool for elucidating underlying mechanisms and for discovering and validating novel therapeutic interventions. Furthermore, multidimensional outcomes measures are possible in animal models, including abdominal pain, anxiety, and altered bowel habits. It is broadly accepted that the clinical relevance of current animal models comes from the observation that chronic stress-associated visceral hyperalgesia is a common concern of patients with IBS. Animal models are often used to examine how chronic psychological stress (through restraint measures and water avoidance) activates the hypothalamic–pituitary–adrenal axis, which is associated with enhanced abdominal pain (visceral hyperalgesia).[15] Other models examine the role of early-life stress (eg, separation of pups from the mother during the suckling phase and limited nesting) and its long-term effects on visceral pain and behavior.[16] Therefore, animal models may provide clues to the pathogenesis of IBS because most models have measurably enhanced visceral nociceptive responses (a surrogate for the hallmark symptoms of visceral hyperalgesia and chronic pain reported by humans with IBS).[17]

In humans, IBS is a female-predominant disorder, but most animal studies of IBS have used only males to avoid the confounding influence of the estrous cycle on outcomes measures, such as visceral pain. The issue of sex differences within the models has received little attention to date, but recent studies in rodents have shown sexually dimorphic effects of early-life stress on visceral sensitivity.[18,19] Thus, future studies should include female animals. Investigators

and funding agencies must acknowledge the need to increase sample sizes (and budgets) to compare data from different stages of the estrous cycle and perform studies comparing males and females.

IBS treatments targeting peripheral epithelial transporters appear to have transitioned successfully from animal models to humans with IBS, at least with respect to transit abnormalities.[20] In addition, the clinical observations of these peripherally acting compounds have been brought back to the bench and defined mechanistically in animal models. Animal models of post-infection (ie, inflammatory) IBS, chronic adult stress induced by water avoidance, and early-life stress are considered highly relevant to human IBS and may facilitate development of novel therapeutics.[21]

Animal models have also proven useful for defining CNS mechanisms of sensitization and nociceptive signaling, as well as for the discovery that chronic stress is an important contributing factor to all aspects of IBS. Chronic stress perpetuates and exacerbates visceral hypersensitivity, abnormal motility, and altered barrier function. For example, in rats, repeated water avoidance stress induces colonic hypersensitivity that is dependent on glucocorticoid receptors within the dorsal root ganglion innervating the lower spinal cord[22,23] or limbic brain areas, such as the central nucleus of the amygdala.[24,25] Transient receptor potential vanilloid type 1 antagonists[26] and central corticotropin-releasing factor receptor antagonists[27] inhibit water avoidance stress–induced colonic hypersensitivity. Experimental models are currently unraveling the epigenetics of IBS[23,25,28] and the plasticity of the CNS after early-life stress.[29] Animal studies are poised to enhance the understanding of brain–gut microbiome interactions in individuals with IBS.[30] Finally, neuroimaging of the CNS, which is now possible in rodent models, will allow direct comparison and translation to human brain imaging, as well as reverse translation to relevant animal models.[31]

Gaps in the current knowledge of the use of animal models to study the pathophysiology of FBDs:

- What are the areas of agreement and disagreement between animal and human studies?
- What is the basis for the observed differences, for example, genetics, epigenetics, or both?
- Can mechanistically focused animal studies (eg, examining the role of biologic sex in FBDs and IBS) be replicated in relevant human tissue samples?
- Can animal models be used successfully for reverse translational research?

Strategies to address the gaps:

- Perform comparative studies on male and female animals to elucidate the mechanisms underlying biologic sex-related differences on clinically relevant outcome measures such as visceral pain (including CNS regions of interest), intestinal barrier function, and the microbiome.
- Perform reverse translation from human brain imaging studies of central biomarkers to suitable animal models (eg, knockout or transgenic models) for further mechanistic evaluations.
- Use appropriate animal models to perform longitudinal (time course) studies to determine whether IBS is a "top-down" or "bottom-up" syndrome (or both) to essentially determine if the CNS is driving the IBS phenotype or if changes in the GI tract are driving changes in the CNS. Interventional studies will help to determine whether changes in the CNS depend on peripheral pathways or develop independently.

Neuromuscular Dysfunction in Functional Bowel Disorders: Neurons, Smooth Muscle, Glia, Interstitial Cells of Cajal, and the Microbiome

Transit through the small and large intestines is slowed in a subset of patients with constipation-predominant IBS and accelerated in a subset of patients with diarrhea-predominant IBS; moreover, dysmotility is reported in a subset of patients with other FBDs.[3,32] Because one goal of therapeutic interventions is to normalize dysmotility,[33] improved understanding of the enteric neuromuscular circuitry in the various forms of FBDs is critical for elucidating their origins and essential for developing more effective treatment strategies. We note that knowledge of the enteric neuromuscular pathophysiology in FBDs is partly limited by the relative paucity of human samples available for ex vivo physiologic analysis. Unlike the mucosa, the deeper layers of the gut are inaccessible by traditional endoscopic procedures, although emerging technologies will likely improve future availability of relevant human tissues.

Motor patterns in the intestines are generated and controlled by intrinsic reflexes of the enteric nervous system (ENS), the critical elements of which include sensory neurons, interneurons, excitatory and inhibitory motor neurons, smooth muscle, glial cells, and interstitial cells.[34–36] Perturbations at any level of this circuitry can disrupt motility. For example, motility that is disrupted by inflammation-induced neuroplasticity persists after recovery from inflammation.[37] In animal models with post-inflammatory symptoms consistent with FBDs,[37] persistent changes in neuronal and motor functions have been identified. Other motility disorders, such as diabetes-associated gastroparesis, constipation, and idiopathic gastroparesis, are associated with observed changes in the interstitial cells of Cajal,[38] and colonic transit can be modulated by disruptions in enteric glial activity.[39]

The ENS can be affected by stress and by enteric bacteria. Stress paradigms that are mediated by corticotropin-releasing factor–expressing enteric ganglia lead to functional changes, such as increased fecal output, increased epithelial secretion and diarrhea, and decreased transepithelial resistance.[40–43] Stress also causes changes in enteric neuronal density and neurotransmitter expression.[41] Enteric bacteria (from the altered intestinal

microbiomes associated with FBDs) are now believed to regulate aspects of the enteric neural circuitry and affect organ functions beyond the intestine.[44]

Numerous studies have demonstrated that soluble mediators found in mucosal biopsies and fecal supernatants from patients with IBS elicit physiologic responses in enteric neurons.[45] In these studies, Ca^{2+}- and voltage-sensitive dyes were used to show that supernatants extracted from IBS biopsy specimens excite enteric neurons. In addition, enteric ganglia could be the target of an immune response in individuals with IBS. A low-grade infiltration of lymphocytes has been observed in the myenteric plexus of full-thickness jejunal biopsy specimens from patients with IBS,[46] and plasma from patients with IBS contains antibodies that target enteric ganglia.[47]

Collectively, these findings provide strong evidence for a role of enteric plasticity in the functional changes that are the hallmarks of FBDs, and further elucidation will likely reveal therapeutic targets (such as the microbiome) that can prevent or reverse these changes.

Gaps in the current knowledge of ENS pathophysiology in FBDs:

- What are the mechanisms responsible for the persistent changes in the enteric neural circuitry after episodes of intestinal inflammation?
- What are the physiologic and neurochemical changes within the enteric ganglia (neurons and glia), the interstitial cell and smooth muscle syncytium, and immune system that occur in response to stress? Do these changes persist after the stress is resolved, as they can with inflammation?
- What are the enteric bacterial products that regulate the enteric circuitry? How do they interact with the neuroepithelial circuit? How are these altered in FBDs?
- Is there an autoimmune component to FBDs that involves the enteric neural circuitry? If yes, what are the physiologic consequences of circulating anti-ENS antibodies?
- What are the mechanisms underlying the differences between IBS bowel habit subtypes?

Strategies to address the gaps:

- Optimize high-throughput approaches to investigate the functions of neurons, glia, interstitial cells of Cajal, and smooth muscle in intact preparations.
- Use advances in enteroid, organoid, and induced pluripotent stem cell engineering to create better in vitro models of human disease.
- Use molecular and cellular approaches to understand the cell-specific alterations in the components of the enteric neural circuitry in FBDs and in animal models of these conditions.
- Determine what combinations of animal models best reflect the human condition in FBDs, and determine how best to use them in translational studies.
- Use current and emerging noninvasive tools to develop an "atlas" of normative data of the human ENS. Use standardized pathologic criteria to define quantitative and qualitative changes in peripheral organs in various FBDs.

Brain–Gut Pathways in Models of Irritable Bowel Syndrome: The Role of Primary Afferent, Efferent, and Spinal Components of the Axis

Although the impact of the brain on gut function has long been known, knowledge of the brain–gut axis has increased substantially only in the past few decades. Now, the brain–gut axis is well understood to be bidirectional and multilayered. Its interconnections are due to the vagal and sacral parasympathetic and sympathetic efferent nerves interacting with the ENS and the visceral enteric intrinsic and extrinsic vagal and spinal afferents that reach higher brain centers. Some evidence suggests that a neuroepithelial circuit also exists, with sensory connections among enteroendocrine cells, enteric neurons, and glia.[48]

Dysregulation of this brain–gut bidirectional neuronal communication is increasingly recognized as the underlying pathophysiology of IBS.[49,50] Dysregulation can be triggered by centrally initiated risk factors (eg, adverse early-life events, anxiety and depression, chronic or acute psychological stress) and by peripheral signals (eg, intestinal infection; dysbiosis; alterations in luminal bile acids, short-chain fatty acids, serotonin [5-HT] release). Despite a rapid expansion in knowledge of fundamental neuronal brain–gut interactions, many aspects remain to be unraveled at the neuroanatomic and molecular levels.

Gaps in the current knowledge of the brain-gut pathways in IBS:

- What is the role of the vagus nerve in the pathophysiology of IBS? Vagal efferent cholinergic signaling suppresses local and systemic pro-inflammatory cytokine levels.[51] Clinical evidence supports impairment of vagus nerve function in IBS.
- What do the interactions among sensory afferents, immune-competent cells, glial cells, and enterochromaffin cells imply about the visceral hypersensitization process?
- What is the cross-talk between intrinsic primary afferent neurons (IPANs) and extrinsic primary afferents in the colon? Although intestinal primary afferent vagal fibers are believed to respond monosynaptically to luminal input, novel evidence in the distal jejunum indicates that bacteria–gut–brain signaling is also mediated by IPANs communicating to vagal afferents through a nicotinic synapse.[52]
- What are the underlying brain–gut neuroendocrine mechanisms involved in chronic stress in adulthood and in early-life adverse events that affect development of IBS?[53]

Strategies to address the gaps:

- Histologically localize classes of colorectal afferent endings (functionally determined mucosal, muscular, and serosal endings).[54]
- Identify the signatures of peripheral mediators involved in the sensitization of IPANs and extrinsic afferents in different experimental models of IBS.[55]
- Define the epigenetic mechanisms underlying long-term sensitization of IPANs and spinal afferents at the level of the dorsal root ganglia and the spinal cord.[23]
- Characterize the role of specific brain loci in bidirectional brain–gut interactions, such as Barrington nucleus in locus coeruleus neurons, which are highly responsive to stress and colorectal distention.[21]

Evidence of Irritable Bowel Syndrome–Related Dysfunctional Circuits in the Human Brain

Although multiple peripheral factors likely have important roles in shaping brain circuitry during development and in adulthood, the brain is ultimately responsible for generating the subjective experience of abdominal pain, discomfort, and anxiety.[56] The brain also influences peripheral target cells in the gut, including the gut microbiome, through the outputs of the autonomic nervous system and the hypothalamic–pituitary–adrenal axis. The intricate involvement of the brain in the bidirectional regulatory pathways of the brain–gut axis make the CNS an attractive source for noninvasive readouts of IBS-symptom–related biologic markers or brain signatures.[57]

Multimodal brain imaging allows standardized evaluation of numerous structural and functional brain parameters by using different scanners at multiple sites. Current imaging techniques include diffusion tensor imaging and structural and resting-state functional imaging. Results from 165 regions of interest and 16 analysis parameters can be generated through semi-automated image-analysis pipelines. Pooled data from multiple sites create sufficiently large datasets suitable for data-driven analyses (eg, supervised and unsupervised machine learning, graph theory, multivariate analyses) to extract quantitative information about resting-state network connectivity, anatomic (white matter) connectivity, and gray matter changes. Such studies have identified alterations in several brain networks relevant to IBS pathophysiology, including the salience, central executive, default mode, sensorimotor, emotional arousal, and central autonomic networks.[58] To date, such cross-sectional analyses have shown moderate correlations with clinical, behavioral, and other biologic parameters.[59]

Gaps in the current knowledge of dysfunctional circuits in the human brain related to IBS:

- Are changes in the gut lumen environment, intestinal barrier function, and peripheral pathways prerequisites for changes in CNS integration and perception? Alternatively, do changes in CNS regions associated with mood and pain registration occur independently? Could both possibilities be true?
- What changes are occurring in the neurochemical coding in the brain circuits involved in IBS? Do changes in the microbiome alter the neurochemical coding?
- Does biological sex have a deterministic role in the neurochemical coding in these brain circuits?
- What is the effect of early-life stress on the neurochemical coding in the brain circuits involved in IBS?

Strategies to address these gaps:

- Develop innovative strategies to address questions of causality, which may lead to the identification of actionable biomarkers.
- Define the neurochemical coding in the brain circuits implicated in IBS.
- Conduct longitudinal imaging studies to facilitate the analysis of moderator and mediator variables.
- Identify the role of gut microbial metabolites and immune parameters that may drive structural brain changes.
- Design pharmacologic intervention studies (eg, interventional phenotyping) to identify brain parameters involved in symptom improvement.

Genetic and Epigenetic Mechanisms and Environmental Factors

An individual's risk of IBS increases if a family member is affected. Studies of twins show that genetic liability and heritability range from 1% to 20% and 0% to 57%, respectively.[60] Genomic studies of IBS, including studies of twins and familial aggregation, have led to the discovery of putative candidate genes that are associated with the clinical disorder, quantitative traits (eg, endophenotypes), or the response to treatment (through pharmacogenomic studies). Candidate gene association studies in IBS have identified proteins involved in GI motor and sensory function, serotonin processing, central and peripheral neural processing, inflammation, intestinal barrier function, bile acid synthesis and processing, and intestinal ion channels.[60,61] Certain single nucleotide polymorphisms have also been associated with quantitative traits in IBS, including GI transit times, cardioautonomic tone, acoustic startle response, and morphologic brain imaging findings.[62–64]

FBDs such as IBS are stress-sensitive disorders, similar to most chronic illnesses. Chronic stress increases an individual's vulnerability to FBD development and symptom exacerbation. Adverse early-life events are associated with an increased risk of physical and mental health disorders and negative health behaviors.[65] Other psychosocial factors that are associated with FBDs include stressful life events in adulthood and psychological states, traits, and comorbidities. Furthermore, maladaptive coping can influence symptom experience, reporting, and health behaviors.[66]

Chronic stress can induce sustained changes in gut motility and sensation. Increased perceptual sensitivity to visceral stimuli is associated with functional and structural changes in regions of the brain involved in sensory processing and modulation, and consequently, patients are more aware of GI symptoms and their contexts. Furthermore, patients with IBS show deficient activation of the inhibitory cortical regions involved in downregulating pain, emotion, and attention during the anticipation and experience of aversive GI stimuli.[67]

Given the stress-sensitive nature of FBDs, epigenetic mechanisms are being actively investigated, particularly in animal models and subgroups of IBS patients, because central and peripheral pathways are regulated by stress-induced modification of gene expression.[23,25,68–70] For example, microRNAs can influence intestinal permeability, and increased transient receptor potential vanilloid type 1 receptor expression and function are associated with visceral hypersensitivity.[68,69] National Institutes of Health initiatives, including the National Institutes of Health Roadmap Epigenomics Mapping Consortium and the 4D Nucleome program, have identified a prominent role for noncoding promoters and enhancers in determining phenotypic subgroups in common, albeit heterogeneous and complex, disorders such as FBDs.[71]

In general, FBDs affect twice as many women as men.[72] Limited data suggest that these sex-associated differences emerge at puberty and persist until midlife. Women with FBDs also report more physical and psychiatric comorbidities and gynecologic pain than women without FBDs.[73] Animal and human studies have demonstrated greater pain sensitivity in females than males.[73,74] Sex-based differences have been observed in the roles of hormones, receptors, and signaling molecules and in the ascending and descending pathways of pain transduction in the spinal cord and brain. Although few clinical trials have been sufficiently powered to detect sex-based differences in treatment response, some IBS treatments may have differential responses based on the patient's biologic sex.

Gaps in the current knowledge of genetic and epigenetic mechanisms and environmental factors associated with FBDs:

- What are the protective factors and risk factors associated with the development of FBDs early and later in life?
- Candidate gene association studies in FBDs have been difficult to replicate or show inconsistent results. Which genes or gene combinations contribute to the widely variant FBD phenotypes?
- How do interactions among genes, the environment, and epigenetic mechanisms affect risk of FBDs and disease pathophysiology?
- How do psychosocial factors increase susceptibility to GI symptoms and symptom flares?
- What is the effect of sex and gender on FBDs? How do puberty, menstrual cycle phase, and perimenopausal and postmenopausal states affect FBD symptoms and pathophysiology?

Strategies to address these gaps:

- Conduct longitudinal studies of children and adults with FBDs, encompassing key time points throughout life. Ensure studies are sufficiently powered to detect sex-based differences and those based on menstrual cycle phase and reproductive stage (ie, puberty through menopause).
- Collect relevant biomarkers and clinical symptoms from multiple time points throughout life.
- Characterize protective factors and risk factors associated with FBDs that develop early and later in life.
- Characterize phenotypes of FBDs and identify genes and gene combinations that contribute to those phenotypes.
- Replicate and confirm genetic studies, especially candidate gene association studies, in larger samples. Encourage multidisciplinary collaboration in gene discovery.
- Examine the interaction of genes and the environment. Investigate the epigenetic mechanisms associated with an increased risk of FBDs and with disease pathophysiology.
- Conduct tissue- and cell-specific studies to evaluate genomic and epigenomic signatures. These signatures potentially can be used to elucidate disease risk, therapeutic risk, and heterogeneity and to predict targeted treatment response.
- Elucidate the effects of psychosocial factors on increasing susceptibility to GI symptoms, symptom flares, and structural and functional brain changes observed in FBDs.

Emerging Role of Dietary Triggers in Irritable Bowel Syndrome

The diagnosis of IBS has traditionally been based on the presence of abdominal pain with altered bowel movements. However, in the past decade, dietary components have emerged as potentially significant triggers of IBS. Patients have suggested that diet has a role in the pathogenesis of the syndrome itself and as a trigger of symptoms, and this view is increasingly held by clinicians and scientists. Putative food intolerances are reported by 20%−70% of patients with IBS, although true allergies are rare.[75] The mechanisms underlying diet and the pathogenesis of IBS suggest possible targets for treatment—mechanisms likely are multifactorial and include triggers on a background of sensitization, either by mechanical distention or physiologic reflexes (eg, fat-induced response, gastrocolic reflex); primary sensitization factors, either by chemical or immunologic means; osmotically active agents; sources of energy capable of modulating the microbial ecosystem in the gut; modulators of intestinal permeability; and factors that

produce psychological aversion because of conditioned reflexes from past experience.[76]

Because of the paucity of mechanistically focused basic science studies and rigorously designed clinical trials, patients follow various diets of unproven benefit. For example, gluten sensitivity is often cited as justification for a restricted diet, but it is unclear whether individuals are reacting to gluten, other components of wheat, or simply to the co-exclusion of fermentable carbohydrates and fermentable, oligo-, di-, monosaccharides and polyols (FODMAPs).[77] FODMAP restriction can ameliorate symptoms and has rapidly been adopted despite concerns about nutritional deficiencies and the lack of long-term data on safety and compliance.[78] Larger multicenter trials are needed to better elucidate the mechanisms involved and to identify the subsets of patients who are more likely to respond to this relatively complex dietary intervention.

Gaps in the current knowledge of the role of dietary triggers in IBS:

- What measures (clinical or biologic) can predict the response to dietary interventions in patients with FBDs?
- What phenotypic characteristics are predictive of response to dietary interventions?
- What are the mechanisms by which a low FODMAP diet reduces FBD symptoms?
- How do wheat and other FODMAPs interact with gut microbiota and mucosal barrier function in the pathophysiology of FBDs?

Strategies to address these gaps:

1. Low FODMAP diet

- Conduct large-scale multicenter studies across diverse populations.
- Increase study durations to evaluate sustainability and long-term nutritional consequences.
- Elucidate the mechanism(s) of action of specific mediators in the FODMAP diet, and reconcile those results with the potential beneficial effects of prebiotics.
- Improve understanding of the differences between FODMAP-responsive and FODMAP-nonresponsive individuals.
- Study the effects of a low FODMAP diet on microbiota, gluten sensitivity, and comorbidities.
- Examine the role of specific foods as "triggers" in the setting of hypersensitivity or as elements that contribute to the pathogenesis of IBS.
- Determine the optimal method of reintroducing FODMAPs into the diet.

2. Gluten sensitivity

- Study the prevalence of wheat sensitivity in patients with IBS.
- Elucidate the components in wheat that produce sensitivity (eg, gluten, amylase trypsin inhibitors).
- Study the roles of microbiota and intestinal permeability in gluten sensitivity.
- Study the effects of gluten sensitivity on comorbidity of IBS, particularly the psychological components.

3. Related issues that require further investigation

- Elucidate the role of immunologic mechanisms in patients with documented food intolerances.
- Rigorously examine the "leaky gut" hypothesis.
- Improve methods to screen and diagnose food sensitivity.
- Improve methods to screen the role of specific food components in individual patients. Narrowing the list of culprit foods will improve compliance and individualize treatments.[79]

Current and Emerging Strategies to Manage Functional Bowel Disorders

FBDs such as IBS are common in children and in adults.[80,81] To date, biomarkers have largely been used only to exclude other organic diseases that mimic IBS. The failure to identify reliable physiologic biomarkers has perpetuated an empiric approach to treatment that is predicated on the patient's predominant symptoms. Given that most medical therapies for IBS target-specific pathophysiologic pathways,[81] treatments theoretically benefit only the subset of patients with IBS whose symptoms are associated with the targeted mechanism. This approach likely explains why clinical treatment efficacy ranges from only 50% to 60%.[82] The therapeutic gain of treatment with medicine (compared with placebo) ranges from 8% to 20%,[82] in part because of the high efficacy of treatment with placebo in the setting of significant psychosocial comorbidity and the subjective manner by which treatment efficacy is measured. The modest therapeutic gain may not be attributable to a lack of efficacy; rather, it may reflect the inability to choose the best treatment for the specific patient. To complicate the issue further, FBDs are costly conditions across all age groups.[83,84] In the current health care market, new treatments must demonstrate value in a phase 3 trial through comparative-effectiveness and cost-effectiveness analyses against existing treatments, not just simple efficacy relative to a placebo. Moreover, because traditional treatments targeting the gut, the brain, or the environment have only modest efficacy, many patients with FBDs, particularly those with comorbidities, explore complementary and alternative treatments.[85,86]

Treatments targeting the GI tract include dietary changes (eg, low FODMAP diet); the use of probiotics in children and adults; and the use of multiple pharmacologic agents, including antispasmodics, serotonin receptors agonists and antagonists, intraluminal antibiotics, chloride channel type 2 activators, guanylate cyclase-C receptor

agonists, and opioid receptor agonist-antagonists (refer to Table 1). Interventions targeting the brain include antidepressants and behavioral therapy (eg, hypnotherapy, cognitive behavioral therapy). Some evidence indicates that educating parents on how to react when their child has abdominal pain may lead to more rapid and complete resolution of the child's symptoms (ie, targeting the environment and learned illness behavior).[87] The roles of acupuncture, herbal preparations, and other complementary and alternative therapies remain poorly defined.

Gaps in the current knowledge of the management of FBDs:

- Can specific biomarkers be identified that are useful for diagnosis and disease management programs? The current methods of symptom-based diagnosis and treatment are inherently limiting. Symptoms will likely continue to serve as the entry point into the management paradigm for IBS, but major treatment advances will not occur until biomarkers can be linked to specific treatment strategies. Some of the most promising targets involve the interaction between early-life events,[88] epigenetics,[89] the microbiome,[90] and downstream metabolomic consequences.
- What are the epigenetic changes and key elements of dysbiosis and metabolomic changes that may predispose patients to FBD development? What constitutes a "normal" microbiome? Microbiome and metabolomic profiling may help to identify patients more likely to respond to dietary interventions (eg, the low FODMAP diet) or to other therapeutic interventions that target the microbiome (eg, antibiotics, probiotics). The genetic background that is conducive to FBD development in general—and IBS in particular—remains to be discovered.[13]
- What is the natural history of different FBDs? How do phenotypes change in the transition from children to adults?
- How do coexisting internalizing disorders and other somatic symptoms affect the response to different therapeutic modalities?

Strategies to address these gaps:

- Develop FBD treatments that are effective in children and adults because many adults with FBDs have symptoms that began in childhood.
- Investigate the role of biomarkers for diagnosing IBS, targeting and monitoring treatment,[86,91] and predicting outcome.
- Conduct gene expression studies to clarify predictors of phenotype and treatment response (ie, individualized treatment).[92] Apply a systems genetics approach to quantitate and integrate intermediate phenotypes, including transcript, protein, and metabolite levels, and gene-by-gene and gene-by-environment interactions.
- Conduct multicenter studies in rigorously phenotyped individuals with FBDs, for example, implement similar inclusion and exclusion criteria, validate symptom questionnaires, standardize collection and testing of samples, and identify quantitative traits (such as intermediate phenotypes or endophenotypes) that may differentiate individuals with FBDs from healthy controls and from patients with other GI conditions that have overlapping symptoms.
- Perform longitudinal studies to determine the natural history of FBDs, identify protective factors and risk factors of FBD development and symptom severity, and establish the predictive value of endophenotypes in symptom severity and treatment response.
- Determine whether the Rome IV diagnostic criteria for FBDs,[93] which includes subgroups of IBS, help increase response rates to therapeutic interventions.
- Better understand how modifications of the gut microbiome affect the GI tract and emotional components of

Table 1. IBS: Current Pharmacologic and Dietary Interventions

Intervention	Main mechanism of action	Effect on the gut
Low FODMAP diet	Decreased osmotic load and colonic distension	Decreased fermentation, changes in the microbiome
Probiotics	Changes in the microbiome	Decreased fermentation, changes in sensation and permeability
Rifaximin	Nonsystemic, minimally absorbed antibiotic	Changes in the microbiome, altered permeability
Lubiprostone	Luminally acting ClC-2 chloride channel agonist	Increased luminal secretion, inhibition of nociceptors
Linaclotide	Luminally acting guanylate cyclase-2C agonist	Increased luminal secretion, inhibition of nociceptors
Alosetron	5-HT_3 antagonist	Decreased visceral pain and secretions, slowed transit
Eluxadoline	Mixed μ- and κ-opioid agonist, and δ-opioid receptor antagonist	Slowed colonic transit, decreased colonic nociception
Antispasmodics, including peppermint oil	Anticholinergics, smooth muscle calcium-channel antagonist	Muscle relaxation, antispasmodic
Tricyclic antidepressants	Serotonin and norepinephrine reuptake inhibitors, anticholinergic and antihistamine effects	Decrease visceral pain, slowed colonic transit
Loperamide, diphenoxylate	μ-Opioid-receptor agonist	Decreased colonic motility, increased fluid absorption

FODMAP, fermentable, oligo-, di-, monosaccharides and polyols; IBS, irritable bowel syndrome.

the FBD symptom complex. Identify those patients who are more likely to respond positively to dietary, probiotic, and antibiotic treatments.[94]

- Identify aspects of the physician–patient relationship that can improve patient satisfaction, adherence to treatment, efficacy of treatment, and other health outcomes.
- Promote and assess programs aimed at improving clinician effectiveness to optimize patient satisfaction, adherence to treatment, and symptom reduction. Evaluate the effect of these programs on health care costs.
- Conduct clinical trials comparing complementary and alternative treatments with conventional therapies. Include patients from infancy through adulthood, with the goal of developing evidence-based integrative treatments.
- Perform augmentation studies using centrally targeted treatments (antidepressants, other neuromodulators, behavioral interventions) to enhance relapse prevention. Recognize that these effects are supplemented by the physician–patient relationship.
- Explore the possible role of apps and wearable or implantable devices for gathering real-time data from individuals with FBDs.

Application of Next-Generation -Omics Technologies to Diagnose and Treat Functional Bowel Disorders: The Road to Precision Medicine

The sequencing of the human genome in 2000 advanced the field of human genomics. It also gave rise to several other "-omics" fields, including epigenomics, proteomics, and metabolomics, and accelerated understanding of the microbiome. One -omics area with direct patient impact is pharmacogenomics.[95,96] Currently, more than 150 medications (13% of the total) have genomic information in their labeling, including several commonly prescribed to treat FBDs.[97,98]

The health care promise of genomics was initially restrained by the high cost of sequencing and a lack of understanding about which of the tens of thousands of variants influenced disease development and which combination of variants were additive or subtractive. However, these issues are being addressed with cost reductions and improved methods.[99,100] With time, variants of genes frequently mutated by positive evolutionary selection will be explored. These variants could be resilience factors, gating the transition from healthy to unwell, rather than disease risk factors per se; such variants would escape detection by genome-wide association studies if considered in isolation.

Gaps in the current knowledge of -omics technologies related to FBDs:

- FBDs have multiple components contributing to their pathogenesis, including complex molecular interactions between genetic, epigenetic, and transcriptional, protein, and secreted factors (ie, the molecular interactome).[23,28,101–105] Can a disease interactome be developed that integrates large datasets derived from high-throughput -omics technologies? Novel therapies can be developed that target the interactome, rather than targeting specific signaling pathways or isolated cell populations.
- How can a systems biology approach to FBDs be implemented? Sophisticated algorithms and software are needed to integrate -omics data.

Strategies to address these gaps:

- Standardized sample collection and storage. Invest in bioethics, bioinformatics, and informational technology. Create well-coordinated biobanks and biorepositories.
- Conduct large-scale collaborative studies with investigators of diverse expertise (eg, -omics technologies and physiologic and imaging studies) to characterize FBD phenotypes, to differentiate FBDs from other diseases, and to sort FBDs into distinct subgroups with potentially different etiology and treatment approaches. Understanding of FBDs and development of new therapeutic strategies would be markedly accelerated by incorporating pharmacogenomics data in clinical trials, depositing all tissue, imaging, physiology, and -omics data from FBD patient studies into a shared database and sharing bioinformatics resources.
- Educate principal investigators and reviewers about the potential role of precision medicine in FBDs. Address the misconception that -omics approaches are useful only for generating hypotheses and not addressing hypotheses.

Summary

A successful approach to advancing FBD research will include the following strategies:

- Performance of vertically integrated studies in relevant animal models and stratified populations of human subjects. Include males and females in the experimental design.
- Elucidation of the bidirectional afferent and efferent pathways and the timing of changes in relevant CNS regions, spinal and enteric pathways, and correlation with specific clinical phenotypes and behavioral end points.
- Establishment of a robust data repository linked to a parallel biorepository with standardized specimen collection and storage. These resources should be validated, shareable, and include relevant control populations.
- Identification, validation, and testing of novel biomarkers for diagnosis and treatment.

- Application of innovative technologies in preclinical and clinical research. Examples include integrated -omics technologies, functional imaging at the cellular and in vivo levels, and gene editing. Dedicated bioinformatics expertise should be available to ensure effective use of the data repository and biorepository for -omics−based research.
- Assessment of value and reproducibility at the preclinical and clinical levels.
- Development of an interdisciplinary approach to elucidate cellular mechanisms and integrated pathways and to monitor therapeutic interventions.
- Performance of longitudinal studies encompassing relevant time points throughout the lifespan (animal and human studies), recognizing that the temporal expression of relevant biomarkers and clinical symptoms is dynamic.
- Evaluation of multimodal therapeutic interventions that are customized for specific patient subpopulations, including pharmacologic, complementary and alternative, and behavioral interventions with the goal of developing evidence-based integrated treatments.
- Initiation of relevant interventions early in life to decrease the risk of FBD development in vulnerable individuals and to improve outcomes of those who have FBDs.
- Promote and assess programs aimed at improving the provider−patient relationship to optimize patient satisfaction, compliance, and symptom reduction. Evaluate the effect of these programs on health care costs.
- Explore the role of web-based applications, wearable or implantable devices for gathering real-time data from individuals with FBDs.
- Development of innovative, multiple-source funding models.

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Conflicts of interest
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