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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