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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

MEETING SUMMARY

2015 James W. Freston Single Topic Conference: A Renaissance in the Understanding and Management of Irritable Bowel Syndrome

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In honor of one of its past presidents, the American Gastroenterological Association (AGA) started the James W. Freston Single Topic Conference, which has been held annually since 2009. The 2015 Freston conference included state-of-the art lectures and posters on current scientific insights in irritable bowel syndrome (IBS; Supplementary Tables 1 and 2), and was organized on behalf of the American Neurogastroenterology and Motility Society and the Neurogastroenterology and Motility section of the AGA. Although the meeting content spanned a wide range of topics, this summary focuses on the scientific advances concerning the prevalence, symptoms, risk factors, biomarkers, and pathophysiology involving brain–gut interactions.

Prevalence and Symptoms

IBS has a global prevalence of 1 in 10 adults[1] and fluctuating symptom patterns of abdominal pain, disturbed defecation, and extraintestinal symptoms. IBS represents a significant health burden owing to direct medical costs and indirect costs. Costs in the United States per patient per year have been estimated to range from $742 to $7547. Men are more likely to report IBS with diarrhea (IBS-D) and women are more likely to report IBS with constipation. Sociocultural factors can influence prevalence, health care–seeking behavior, symptoms, and treatment response.

The worldwide prevalence of pediatric IBS is 13.5%; childhood functional abdominal pain disorders including IBS increase the risk for adult functional gastrointestinal disorder (FGIDs). Thus, approximately 40% of children with functional abdominal pain will become adults with either IBS or another FGID and 40% will continue to suffer from an anxiety disorder into adulthood.

IBS is a heterogeneous and multidimensional disorder. The underlying physiologic and psychological determinants of symptoms vary and, without an understanding of these determinants, treatment can be nonspecific and varies in its success. An updated classification system for IBS, the Rome IV diagnostic criteria, along with a multidimensional clinical disease profile to aid in clinical management was released in May 2016.

Risk Factors

Genetics

A heritable component of IBS is supported by family and twin studies and a Swedish proband study. To date, there have been limited findings in candidate gene studies; one of the fundamental flaws has been the need for ≥2000 patients to achieve the *P* values of 10^{-7} typically required in genetic association studies. One exception is *TNFSF15* gene, which is associated with risk of IBS in several European and US cohorts.[2] The first genome-wide association study of IBS in 5466 individuals from a Swedish population-based (twin) cohort, identified 1 locus at 7p22.1, which includes the genes *KDELR2* (KDEL endoplasmic reticulum protein retention receptor 2) and *GRID2IP* (glutamate receptor, ionotropic, delta 2 [Grid2] interacting protein), which showed consistent IBS risk effects.[3] This finding was replicated in 6 case-control cohorts from Europe and the United States. Currently, a collaborative project is examining genetics of IBS in >30,000 European population-based cohorts, and in well-characterized IBS patients and controls from Europe and the United States.

The feasibility of identifying genetic variants by risk allele frequency and strength of genetic effects is shown in Figure 1. IBS may be caused by a number of relatively common alleles, each of which increases the risk of disease by a small percentage. However, there are also limitations of exome DNA sequencing alone, for example, failure to appraise epigenetics or tissue protein expressions resulting from the genes. Progress in genetic association studies relies heavily on accurate phenotyping, which currently depends primarily on symptoms. The imprecision of a symptom-

Abbreviations used in this paper: **AGA, American Gastroenterological Association; BA, bile acid; EALs, early adverse life events; FGID, functional gastrointestinal disorder; IBS, irritable bowel syndrome; IBS-D, IBS with diarrhea; SCFA, short chain fact acid; TRPV, transient receptor potential vanilloid.**

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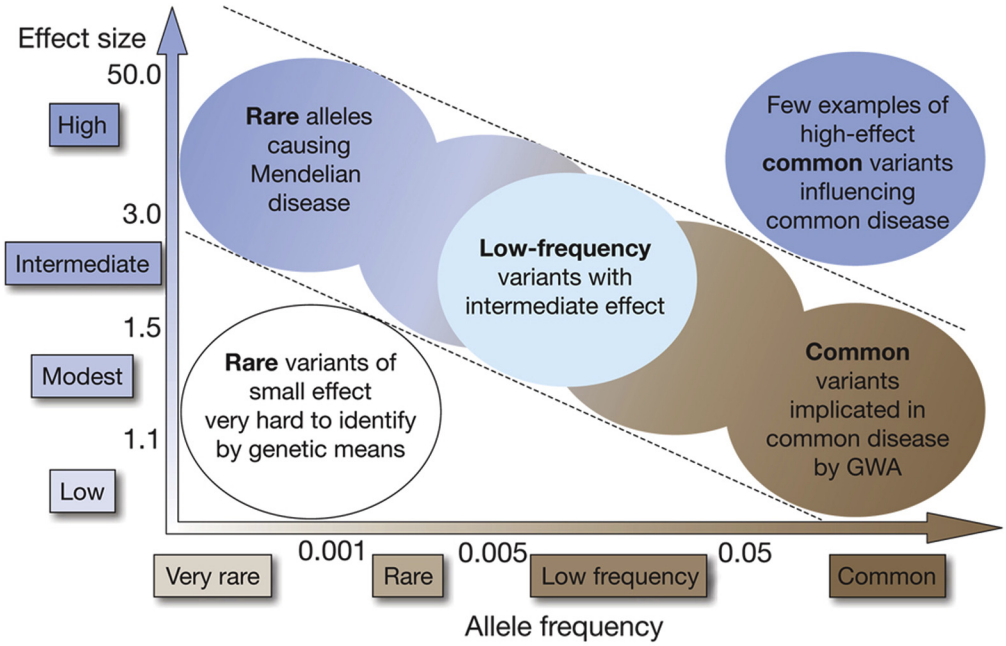

Figure 1. Feasibility of identifying genetic variants by risk allele frequency and strength of genetic effect (odds ratio).[4] There is a relationship between the allele frequency and effect size and the methods that are most appropriate for discovering gene–disease relationships.[4] Mendelian disorders (*upper left*) are typically caused by very rare alleles with a large effect size. This method requires large pedigrees available for testing and does not pinpoint the disease causing allele but a region that may contain hundreds of candidate genes. Other diseases (*lower right*) may be caused by a number of relatively common alleles, each of which increases the risk of disease by a small percentage. This class of disease has been studied with large case-control association studies, which search for the difference in allele frequency of polymorphic markers between unrelated groups of affected and unaffected individuals or within families. GWA, genome-wide association.

based diagnosis may have contributed to slow progress in genetic studies. Some advances in genetics and pharmacogenetics have resulted from the use of endophenotypes, such as colonic transit measurements or brain signatures.

Combined Genetics and Expression

The heterogeneity and complexity of IBS requires use of multiple types of –omics approaches (eg, whole exome/genome sequencing, transcriptomics, proteomics, metabolomics, epigenomics, brain connectome, etc) that allow assessment of various mechanistic networks. Thus, it is important to characterize the IBS phenotype using standardized symptom measures in conjunction with historical information about environmental exposures, early life stress, and medical history to capture potential epigenetic influences, and to obtain other quantitative variables such as diet, physiologic measurements, and microbiome.

Advances in bioinformatics will facilitate the creation of the databases needed to understand complex intracellular and intercellular networks, linkage analyses, and association analyses needed to find the missing heritability component of IBS.[4] Using these data and new integrated analytic platforms, it is anticipated that pathways and networks may unmask the pathogenesis of IBS and ultimately lead to a paradigm shift toward systems medicine.[5] The field of IBS is just starting to exploit genome-wide association studies, exome DNA sequencing, RNA sequencing, and expression studies of small intestinal and colonic mucosa.

Diet

Up to 70% of patients with IBS identify certain foods as symptom triggers, although linkage with a clear pathophysiologic mechanism has not been identified. Studies have shown that patients commonly identify trigger food groups including high fiber foods, poorly absorbed carbohydrates, also known as fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs), gluten, dairy, high fiber foods, fatty foods, spicy foods, caffeine, and alcohol.

Randomized controlled trials have demonstrated a significant decrease in overall symptoms, especially for IBS-D patients, with a low FODMAP diet, although this was not superior to traditional dietary advice in a recent randomized controlled trial.[6] It is unclear how these diets reduce symptoms or impact symptom severity. Although gluten was previously thought to be a specific IBS food trigger, a recent study did not support this when FODMAPs were also excluded.[7]

Celiac disease, a chronic inflammatory condition of the intestine triggered by exposure to gluten in patients with a particular susceptibility, can produce symptoms that mimic IBS. Evidence suggests that, in most populations, symptoms of IBS are not a predictor of hidden celiac disease, which is present in approximately 1% of the Caucasian population. In the presence of other risk factors, testing for celiac disease is justifiable, because the overlap IBS with symptoms may be treatable by gluten withdrawal.

Early Adverse Life Events and Stress

IBS is a stress-sensitive disorder.[8] Stressful life events in childhood (early adverse life events [EALs]) and/or adulthood have been shown to be associated with the onset of, and symptom exacerbations, in IBS. Based on rodent and human studies, EALs may increase the susceptibility to IBS by contributing to reported abnormalities, including increased visceral sensitivity, altered brain signatures, intestinal permeability, colonic motility, stress responsiveness, and altered gut microbiota. Long-term effects of EALs may be owing to epigenetic modulation of gene expression, which can result in a change in phenotype without altering genotype. For example, methylation of the glucocorticoid receptor gene is associated with decreased glucocorticoid receptor messenger RNA, and increased hypothalamic–pituitary–adrenal activity, and visceral hypersensitivity in animal models is associated with knockdown of glucocorticoid receptors in the amygdala.[9]

A dysregulated hypothalamic–pituitary–adrenal axis has been found in IBS patients compared with healthy controls; however, findings are inconsistent (increased, blunted, or normal) at baseline or in response to stressors or hormone stimulation.[8] Potential factors involved in the varied responses include sex, EALs, glucocorticoid resistance, and hyperdrive of corticotropin-releasing factor pathways.

Peripheral Mechanisms of IBS

Motility and Transit

Diverse transit (radiopaque markers, scintigraphy, wireless motility capsule) and intraluminal measurements of phasic pressure activity profiles (such as increased high amplitude propagating contractions in IBS-D) and colonic tone and compliance provide evidence of motor abnormalities in IBS-D and IBS with constipation.

Visceral Hypersensitivity

Increased perception of chemical and mechanical stimuli (visceral hypersensitivity) in IBS may be related to aberrant function of extrinsic afferents, central augmentation of visceral afferent signals, or both. Low-grade mucosal immune activation (especially in postinfectious IBS), reflected in increased activation of mucosal mast cells and release of mediators (such as histamine, serotonin, and proteases) may contribute to visceral afferent hypersensitivity. Based on animal studies, inflammatory and mast cell mediators, such as PAR2 receptors, nerve growth factor, ion channels, histamine, and bile acids (BAs), affect afferent nerve function through their interactions with nociceptors such as transient receptor potential vanilloid (TRPV)1, TRPV4, and TRPA1.[10]

Visceral Cross-Talk

Epidemiologic and clinical studies show overlap of bowel, bladder, and reproductive organ pain in a subgroup of patients. Both existing and latent pelvic conditions can enhance the degree of pain experienced in adjacent pelvic organs when irritated acutely. Sensory innervation of these pelvic organs is connected functionally and structurally.[11] Peripheral mechanisms include nociceptor activation in adjacent organs from inflammatory mediators present after peripheral insults, changes in dorsal horn neuron responsiveness, and intraganglionic/intraaxonal interactions. Centrally mediated mechanisms recently implicated in such comorbidity include shared alterations in the salience and the sensory motor networks.[12]

Immune Function

Differences in immune function in blood and gut mucosa between IBS patients and healthy controls have been reported, but data are inconsistent and difficult to interpret, in part owing to methodologic issues, and any correlation with symptoms is modest. Alterations in certain T lymphocytes ($CD25^{+}$) in blood and gut mucosa are associated with IBS symptoms. B cells homing to the gut are associated with abdominal pain in children with IBS and stool frequency in adults with IBS.[13] Enteroendocrine cells play a role in activation of the immune response leading to visceral hyperalgesia.

Microbiome

Direct and indirect pathways link intestinal microbiota, intestinal epithelial cells, immune cells in the lamina propria, and the nervous system and likely play a key role in the maintenance of homeostasis or the development of disease (Figure 2).[14] Sequencing studies have described alterations in the intestinal microbiota of IBS patients that may contribute to dysbiosis, and contribute to local and extraintestinal IBS symptoms.

Recent data demonstrating that intestinal microbiota can influence brain development, neurochemistry, and cognitive and emotive functions have prompted consideration of a microbiota–gut–brain axis. This axis has been implicated in the pathogenesis of a spectrum of disorders including intestinal and psychiatric diseases. For example, colonization of adult germ-free maternally separated (stressed) and control mice with the same microbiota produces distinct microbial profiles, which are associated with altered behavior only in the maternally separated mice, suggesting an association of early life stress induced physiologic changes, intestinal dysbiosis, and abnormal behavior.[15] Rodent models have shown that changing the microbiota through antibiotics, colonizing germ-free mice with specific microbiota, or exposing them to EAL induces changes in host physiology and ultimately behavior.[12,16]

Gut Barrier

A defect in the intestinal barrier seems to play a pathogenic role in IBS; patients with increased intestinal permeability have higher FGID severity scores and visceral hypersensitivity, possibly linked to altered expression and function of specific intestinal epithelial tight junction proteins resulting in increased paracellular permeability to macromolecules.[17]

BAs and Short Chain Fatty Acids

Alterations in total and individual fecal BAs and short chain fact acids (SCFAs) have been implicated in the

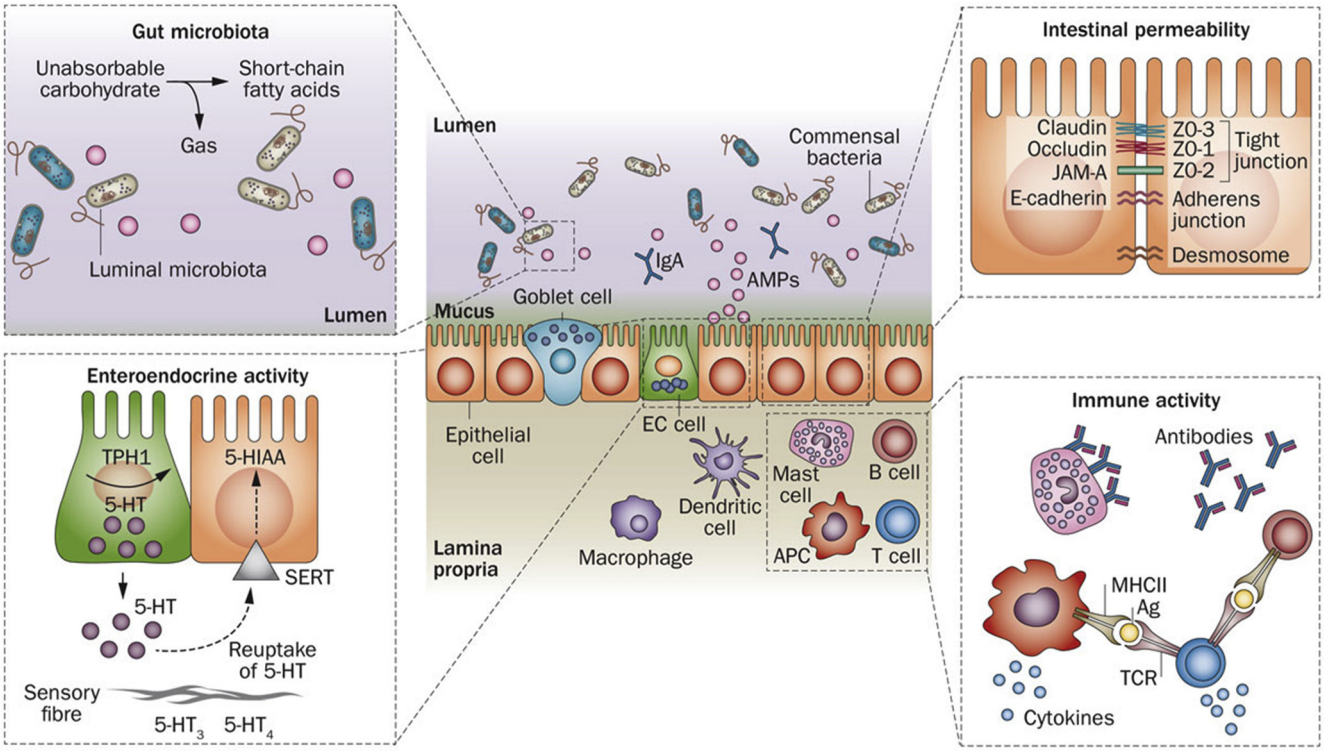

Figure 2. Summary of peripheral factors involved in the pathophysiology of irritable bowel syndrome (IBS).[14] Factors including gut microbiota, increased intestinal permeability, altered balance in enteroendocrine system, and a dysregulated immune system in the gut likely have important roles in the development of IBS, although details on how they interact in IBS is not known. 5-HIAA, 5-hydroxyindole acetic acid; 5-HT, 5-hydroxytryptamine; Ag, antigen; AMP; antimicrobial peptide; APC, antigen presenting cell; IgA, immunoglobulin A; JAM-A, junctional adhesion molecule-A; SERT; 5-hydroxytryptamine transporter; TCR, T-cell receptor; TPH1, tryptophan hydroxylase 1; ZO, zonula occludens.

pathogenesis of IBS. BA malabsorption is recognized increasingly among patients (25%-40%) with chronic diarrhea or IBS-D. There are increased levels of primary fecal BAs in IBS-D with reduced levels of nonsecretory BAs in IBS with constipation. Administration of the BA sequestrant colesevelam delays colonic transit in IBS-D. Conversely, acceleration of colonic transit was observed with an ileal BA transport inhibitor (elobixibat) in chronic constipation. BA malabsorption may result from deficiency in ileal enterocyte production of the hormone fibroblast growth factor-19, which downregulates the synthesis of BAs in hepatocytes. Genetic factors involved in BA diarrhea include variations in the gene for the BA receptor, *TGR5,* or genes involved in BA synthesis such as *Klotho B* and *FGFR4*.[18]

Major SCFAs (eg, acetate, propionate, and butyrate) result from metabolism of dietary carbohydrates by colonic bacteria. Fecal SCFA levels and profile may be associated with IBS phenotype, colonic transit, and visceral hypersensitivity. The relationship of dysbiosis in the intestinal microbiota and changes in intraluminal organic acids such as SCFAs or BAs are currently being studied in IBS.

Central Mechanisms

Brain imaging modalities used in IBS include functional and structural imaging modalities. Functional modalities include functional magnetic resonance imaging (MRI) to study evoked brain response during a task (eg, rectal distension) and during the resting state; structural modalities include imaging of grey matter and white matter properties. Differences exist between IBS and healthy controls in the regional connectivity of brain networks and changes in the architecture of functional and anatomic brain networks. Brain networks show correlations with nonbrain parameters, including clinical, genetic, immunologic, and gut microbiota-related factors.[5] Multimodal imaging (eg, resting state functional MRI, structural MRI, diffusion tensor imaging and MRI [MR spectroscopy]) and multiple types of analyses are recommended to provide a comprehensive view of the brain in IBS. Future longitudinal studies in large, well-phenotyped individuals using systems biological analyses are required to confirm current concepts, and identify novel treatment targets within the brain–gut–microbiome axis. Reverse translational studies in suitable animal models will help to confirm functional brain imaging findings and correlate them with actual changes in neurotransmitter expression and function. This represents a potentially useful application of optogenetics to improve our understanding of altered brain function.

Biomarkers

Over the last 2 decades, research has led to an appreciation of a variety of central and peripheral mechanisms that

Table 1. Potential Etiological Mechanisms as Biomarkers for Irritable Bowel Syndrome[19–21]

Symptom responses to nutrient and lactulose challenge.
Methane detected during the lactulose breath test.
Circulating lymphocyte-stimulated or monocyte-inhibited expression of cytokines.
Polymorphisms in genes encoding cytokines.
Decreased rectal mucosal interleukin-10 messenger RNA expression.
Density of duodenal chromogranin A-expressing cells.
Neuroendocrine abnormalities.
Serotonin.
Gut microbial changes.
Increased epithelial permeability.
Colonic transit.
Bile acids (retention, synthesis, excretion).
Mucosal expression (eg, barrier, immune, neurotransmitter, ion transport mechanisms).
Structural and functional brain imaging signature profiles.

initiate or perpetuate perturbations of gastrointestinal motor and sensory functions and lead to IBS symptoms. Symptom-based criteria are insufficient biomarkers. IBS requires actionable diagnostic and therapeutic outcome biomarkers that incorporate advances in genetics, mucosal protein expression, microbiota, and the metabolome, and brain imaging. Current candidate biomarkers are shown in Table 1.[19–21] Some are already actionable (eg transit, BAs, serotonin). Future research will address microbial diversity and interactions with the host genome to better understand the pathobiology of IBS and lead to more targeted therapeutic approaches.

Future Directions

1. We are in the midst of a rapid discovery phase in IBS research as it applies to pathophysiology and diagnosis of this heterogeneous disorder. Cutting-edge research tools and techniques should be used to study future areas of research, including –omics with a personalized approach, advanced brain imaging techniques, translational animal models, better phenotyping of IBS patients to study mechanisms and guide treatment, and the development of biomarkers and predictors of diagnosis, treatment response, and safety. Future research will include collection of real-time data longitudinally, from the host and from the gut microbiome. It is expected that multiomics profiling may reveal dynamic biomolecular signatures during times of perturbation and enhance our understanding of the system-wide biochemical and cellular changes that occur during environmental exposures.

2. Experimental models and translational research in human tissue samples are required to enhance our understanding of the relationship between the intestinal barrier and the immune system, intestinal microbiota, visceral hypersensitivity, food triggers and stress.

3. The quest for practical diagnostic and actionable biomarkers will need to continue to individualize diagnosis and optimize treatment of patients with IBS. The National Institute of Diabetes and Digestive and Kidney Diseases conducted a workshop on June 23-24, 2016, to identify future areas of research for FGID and the most effective and strategic research approaches to study them (available: www.niddk.nih.gov/news/events-calendar/Pages/fbdworkshop2016.aspx#tab-agenda).

4. Given the need to precisely define and classify the symptom clusters of IBS and other FGIDs to acquire homogeneous patient groups for clinical research and clinical trials, we anticipate (a) simplifying some symptom-based criteria, (b) improving diagnostic algorithms to guide clinicians, and (c) addressing the severity and variability of intestinal and extra-intestinal symptoms to create an individualized treatment plan for the patient.

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Conflicts of interest
These authors disclose the following conflicts: Lin Chang has served on scientific advisory boards for Takeda, AstraZeneca, Allergan, QOL Medical, Ardelyx, Synergy, Commonwealth Laboratories, and Ironwood, Synthetics Biologics, and IM Health Science. John Wiley is recipient of a research grant from Takeda Pharmaceuticals. Michael Camilleri has received research support in the field of IBS in the past 3 years from Tsumura, Salix, and EnteraHealth, and he has done consulting in the field of IBS in the past 3 years with GlaxoSmithKline with remuneration to his employer, Mayo Clinic. The remaining author discloses no conflicts.

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Supplementary Materials

Supplementary Table 1. Meeting Program

Course Co-Directors: Lin Chang and Margaret Heitkemper

Scientific Planning Committee: Lin Chang, Margaret Heitkemper, Michael Camilleri, John Wiley

Session 1: Setting the Stage for the Renaissance of IBS and Moving Beyond

Moderators: Lin Chang, Anthony Lembo

Title	Speaker
Economic Burden and Worldwide Prevalence in Men and Women with IBS	Alexander Ford
Does Pediatric IBS Predict Adult IBS?	Miranda van Tilberg
Symptom-Based Diagnosis of IBS: Where Might We Go?	Douglas Drossman
Diagnostic and Therapeutic Implications of Advances in IBS	Michael Camilleri

Session 2: Genetics: Where Are We and Where Might We Go?

Moderators: Margaret Heitkemper, Michael Camilleri

Session Name	Speaker
Personalized Medicine based on Personal Omics Profiling	Michael Snyder
Exome and RNA Sequencing Methodology: Applications in IBS	Martin Martin
Multi-center Genome-wide Association Studies in IBS	Mauro D'Amato
Defining the Essentials of the Phenotype and Quantitative Traits	William Whitehead
Discussion	

Session Name	Speaker
Keynote Lecture: Lessons Learned-Building a Research Network for IBS	Frank Hamilton

Session 3: Motility and Sensory Abnormalities in the Colon and Pelvis

Moderators: Satish Rao, Emeran Mayer

Session Name	Speaker
Evidence of the Utility of Colonic Motility/Transit Measures in IBS	Satish Rao, MD,
Mechanisms of Visceral Hypersensitivity	Guy Boeckxstaens
Mechanisms of Overlapping Pelvic Pain Disorders	Frank Tu

Session 4: Luminal Factors Affecting Epithelial Function and Symptoms in IBS

Moderators: William D. Chey, Jasmine Zia

Session Name	Speaker
Food Intolerances in IBS: Real or Imagined?	Elena Verdu
Gluten Intolerance and/or Celiac Disease: Implications in IBS	Joseph Murray
Bile Acids and Short Chain Fatty acids	Andrea Shin

Session 5: Peripheral Neuroimmune Measures in the Gut: Plausible Biomarkers for IBS?

Moderators: Beverly Greenwood van Meerveld, Guy Boeckxstaens

Session Name	Speaker
Mucosal Barrier Function: Role in IBS	Beverly Greenwood van Meerveld
Immune Activation: Role in IBS	Rob Shulman
Signaling between Microbiota and Epithelial Cells: Is It Relevant to IBS?	Charalabos Pothoulakis

Poster Session (Supplementary Table 2)

Session 6: Brain–Gut Interactions in IBS

Moderators: John Wiley, William Whitehead

Session Name	Speaker
Role of Stress and Early Life Trauma in IBS	Lin Chang
Gut Microbiota-Brain Interactions in IBS	Permysl Bercik
Toolkit for brain imaging in IBS	Jennifer Labus
Central Networks: Signature Files for IBS	Emeran Mayer

Session 7: Current and Emerging Treatments in IBS

Moderators: Lin Chang, Laurie Keefer

Session Name	Speaker
Exclusionary Diets Including Low FODMAPs – Do They Work?	Jasmine Zia
Targeting the Microbiome	William D. Chey
Central and Peripheral Targets	Anthony Lembo
Behavioral Therapies: What's New?	Laurie Keefer
Thinking Outside the Box – The Future of IBS	John Wiley

Supplementary Table 2. Poster Presentations:

Immunological and Psychological Abnormalities in Patients With Irritable Bowel Syndrome

Sofia Belous[*], Scientific Centre for Coloproctology, Moscow, Russia

The Role of the Glucocorticoid Receptor in the Regulation of Stress-Induced Nociception; Implications for Irritable Bowel Syndrome

Rachel D. Moloney PhD, University of Oklahoma Health Sciences

A Novel Formulation Containing a L-Menthol and Peppermint Oil Blend (LPB) Reduces Symptom Intensity and Frequency in Irritable Bowel Syndrome (IBS)

Michael Epstein, MD, Digestive Disorders Associates, Annapolis, Maryland

Cat Dander Sensitization - The Link Between IBS & Asthma

Kewin Tien Ho Siah, MBBS[*], National University Health System Singapore

Physiological Correlates of Perceived Stress in Patients with IBS

Kristen Weaver, ACNP, ANP[*], College of Nursing, National Institute of Nursing Research (NINR)

Nutritional Management of Refractory IBS-D patients by the Medical Food Serum-Derived Bovine Immunoglobulin (SBI) in a 28-Patient Cohort

Hayley Young, PhD, Entera Health

Why Irritable Bowel Syndrome (IBS) and Functional dyspepsia (FD) are Immuno-neuronal Disorders of Mucosal Cytokine Imbalances Reversible with Polymerized Cross-linked Sucralfate

Ricky W. McCullough, MD, MSc, Mueller Medical International

Context of Uncertainty Modulates Brain Activity During Rectal Distension in IBS

Michiko Kano, Tohoku University

5-HT3 Receptor Signaling is a Rat Model of Sex Specific Visceral Hypersensitivity

Nadine El-Ayache, BS[*], Michigan State University

Anxiety Symptoms Mediate the Relationship Between Adverse Childhood Experiences and Irritable Bowel Syndrome

Elizabeth J. Videlock, MD[*], David Geffen School of Medicine at UCLA

Effects of Emotional Awareness and Expression Training Versus Relaxation Training for People With Irritable Bowel Syndrome: A Randomized Trial

Elyse R. Thakur, PhD[*], Wayne State University

Night Time Heart Rate Variability and Its Relationship to Pain Sensitivity and Gastrointestinal Symptoms Differ by /irritable Bowel Syndrome Bowel Pattern Group

Monica E. Jarrett, PhD, RN, Dept. of Biobehavioral Nursing and Health Systems University of Washington, Seattle

Feasibility of Measuring the Contractile Electrical Complex Over 72 hours in a Healthy Human Subject Using a Wearable, Wireless Electrode Patch.

Anand Navalgund, PhD[*], G-Tech Medical

[*] *Junior investigator travel award.*