Personalised nutrition and functional digestive disorders: taking the BS out of IBS!

Benjamin I. Brown, ND

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Affiliations and disclosures

Affiliations:

Director, the Nutritional Medicine Institute (www.NMI.health)

Disclosures:

I am a consultant for Pure Encapsulations, which supply food supplements and nutrigenomic testing.

I am director of the Nutritional Medicine Institute, which receives sponsorship from food supplement companies and functional laboratories.

I receive loyalties from the book The Digestive Health Solution.

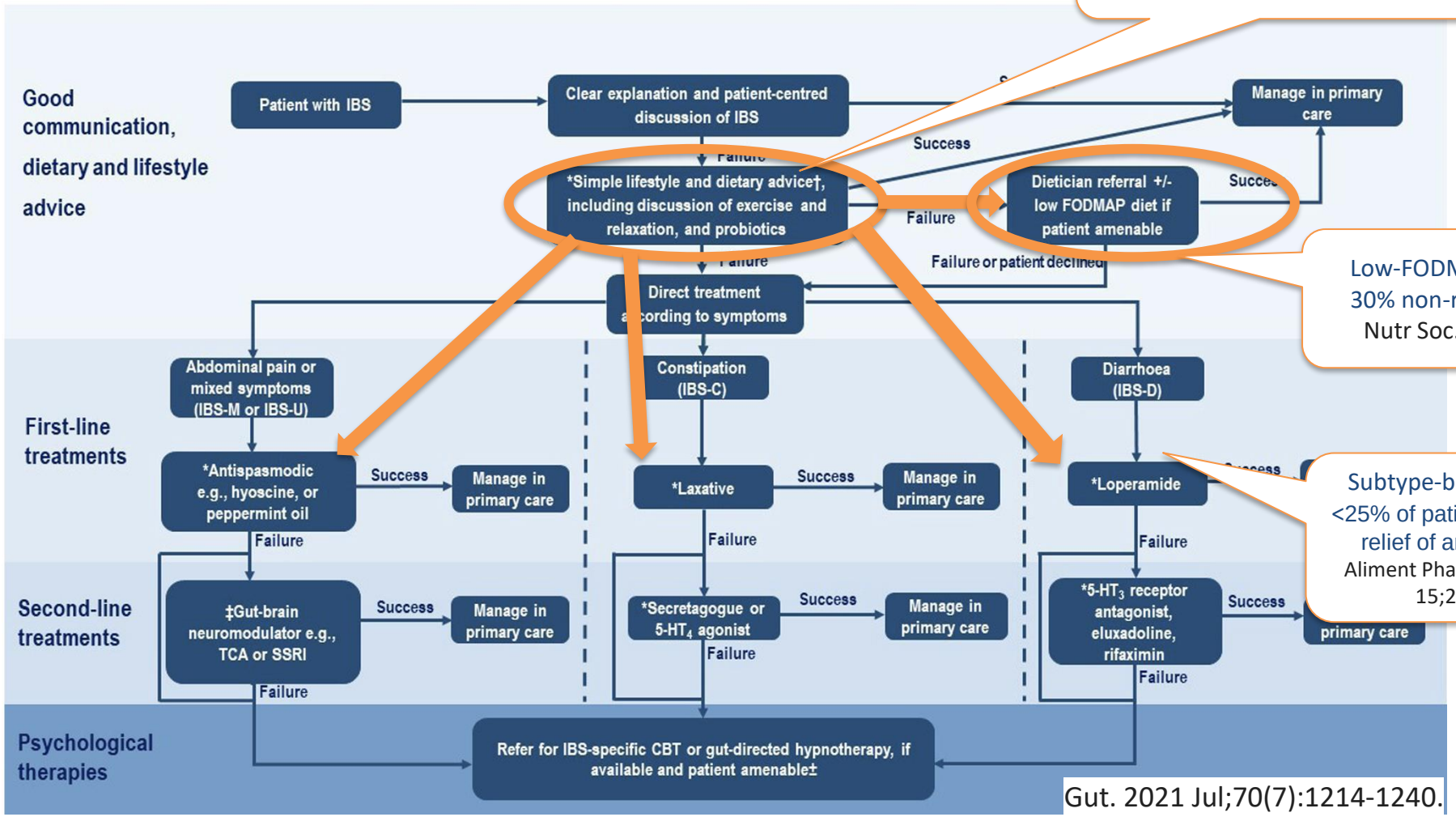
I have no other relevant conflicts of interest to disclose.

"Symptomatic treatment, no matter how "natural," is rarely good medicine. As long as the fundamental cause continues unaddressed because only some symptoms have been relieved, the person gets sicker and sicker."

– Joseph Pizzorno, ND.

How are people with IBS managed?

NICE/ BDA traditional IBS diet has circa 50-60% non-responders.* BMC Med. 2022 Sep 13;20(1):287.



Low-FODMAP diet has circa 30% non-responders.* Proc Nutr Soc. 2023 Jul 7:1-11

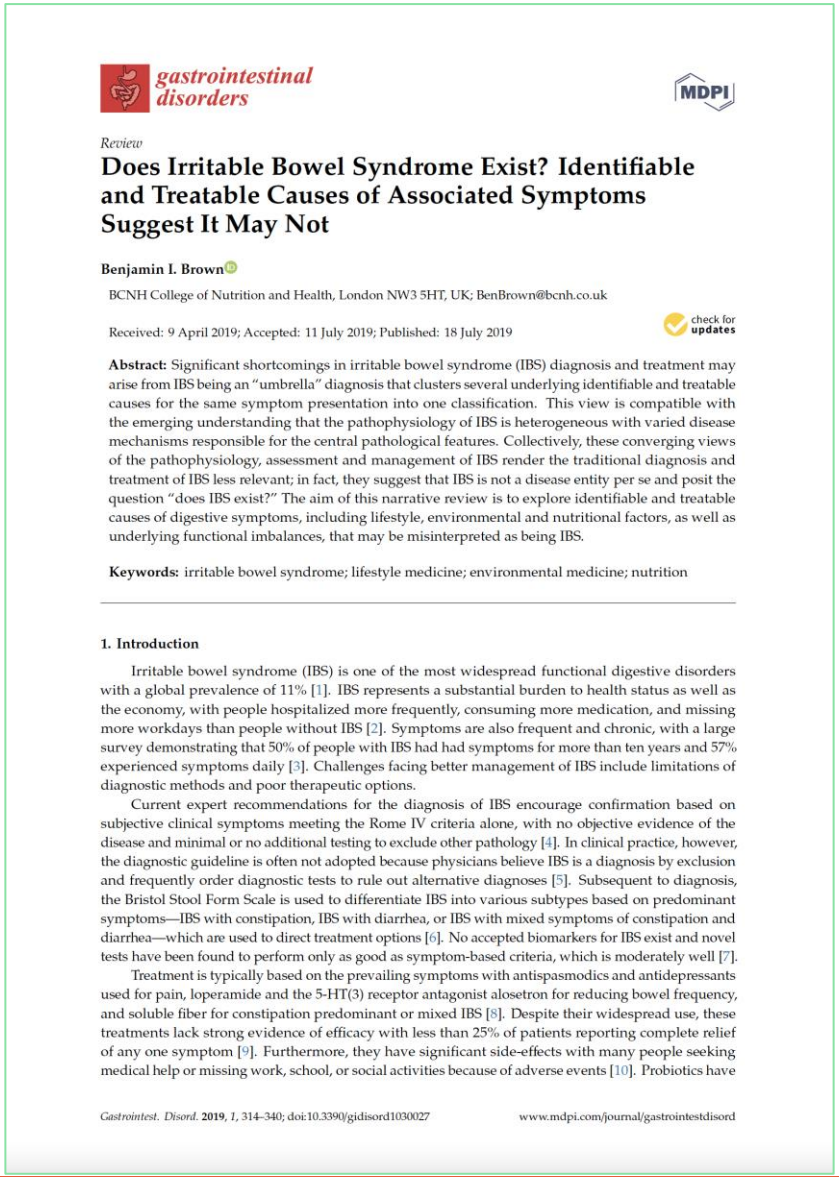
Subtype-based management <25% of patients report complete relief of any one symptom.* Aliment Pharmacol Ther. 2006 Jul 15;24(2):183-205.

Gut. 2021 Jul;70(7):1214-1240.

One disease, or many?

"Significant shortcomings in irritable bowel syndrome (IBS) diagnosis and treatment may arise from **IBS being an "umbrella" diagnosis that clusters several underlying identifiable and treatable causes** for the same symptom presentation into one classification."

Gastrointest. Disord. 2019, *1*(3), 314-340



gastrointestinal disorders

MDPI

Review

Does Irritable Bowel Syndrome Exist? Identifiable and Treatable Causes of Associated Symptoms Suggest It May Not

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Received: 9 April 2019; Accepted: 11 July 2019; Published: 18 July 2019

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Abstract: Significant shortcomings in irritable bowel syndrome (IBS) diagnosis and treatment may arise from IBS being an "umbrella" diagnosis that clusters several underlying identifiable and treatable causes for the same symptom presentation into one classification. This view is compatible with the emerging understanding that the pathophysiology of IBS is heterogeneous with varied disease mechanisms responsible for the central pathological features. Collectively, these converging views of the pathophysiology, assessment and management of IBS render the traditional diagnosis and treatment of IBS less relevant; in fact, they suggest that IBS is not a disease entity per se and posit the question "does IBS exist?" The aim of this narrative review is to explore identifiable and treatable causes of digestive symptoms, including lifestyle, environmental and nutritional factors, as well as underlying functional imbalances, that may be misinterpreted as being IBS.

Keywords: irritable bowel syndrome; lifestyle medicine; environmental medicine; nutrition

1. Introduction

Irritable bowel syndrome (IBS) is one of the most widespread functional digestive disorders with a global prevalence of 11% [1]. IBS represents a substantial burden to health status as well as the economy, with people hospitalized more frequently, consuming more medication, and missing more workdays than people without IBS [2]. Symptoms are also frequent and chronic, with a large survey demonstrating that 50% of people with IBS had had symptoms for more than ten years and 57% experienced symptoms daily [3]. Challenges facing better management of IBS include limitations of diagnostic methods and poor therapeutic options.

Current expert recommendations for the diagnosis of IBS encourage confirmation based on subjective clinical symptoms meeting the Rome IV criteria alone, with no objective evidence of the disease and minimal or no additional testing to exclude other pathology [4]. In clinical practice, however, the diagnostic guideline is often not adopted because physicians believe IBS is a diagnosis by exclusion and frequently order diagnostic tests to rule out alternative diagnoses [5]. Subsequent to diagnosis, the Bristol Stool Form Scale is used to differentiate IBS into various subtypes based on predominant symptoms—IBS with constipation, IBS with diarrhea, or IBS with mixed symptoms of constipation and diarrhea—which are used to direct treatment options [6]. No accepted biomarkers for IBS exist and novel tests have been found to perform only as good as symptom-based criteria, which is moderately well [7].

Treatment is typically based on the prevailing symptoms with antispasmodics and antidepressants used for pain, loperamide and the 5-HT(3) receptor antagonist alosetron for reducing bowel frequency, and soluble fiber for constipation predominant or mixed IBS [8]. Despite their widespread use, these treatments lack strong evidence of efficacy with less than 25% of patients reporting complete relief of any one symptom [9]. Furthermore, they have significant side-effects with many people seeking medical help or missing work, school, or social activities because of adverse events [10]. Probiotics have

One way to personalise, or many?

"Identifying predictors of response to dietary therapy is an important goal as **management could be tailored to the individual to target specific dietary components**, and thereby reduce the level of dietary restriction necessary."

Neurogastroenterol Motil. 2018 Jan;30(1). doi: 10.1111/nmo.13238.

Received: 28 August 2017 | Accepted: 27 September 2017
DOI: 10.1111/nmo.13238

REVIEW ARTICLE

WILEY Neurogastroenterology & Motility NGM

Dietary therapies for functional bowel symptoms: Recent advances, challenges, and future directions

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Funding information
This work was supported by the Canadian Institute of Health Research (CIHR), IMAGINE Strategy for Patient-Oriented Research (SPOR)

Abstract

Background: Functional gastrointestinal symptoms in irritable bowel syndrome (IBS) and quiescent inflammatory bowel disease (IBD) cause significant morbidity and a reduction in quality of life. Multiple dietary therapies are now available to treat these symptoms, but supporting evidence for many is limited. In addition to a further need for studies demonstrating efficacy and mechanism of action of dietary therapies, the risk of nutritional inadequacy, alterations to the microbiome and changes in quality of life are key concerns requiring elucidation. Identifying predictors of response to dietary therapy is an important goal as management could be tailored to the individual to target specific dietary components, and thereby reduce the level of dietary restriction necessary.

Purpose: This review discusses the available dietary therapies to treat symptoms in patients with IBS and patients with quiescent IBD suffering from IBS symptoms, with the aim to understand where current dietary evidence lies and how to move forward in dietary research in this field.

KEYWORDS
diet, dietary therapy, functional bowel disorders, inflammatory bowel disease, irritable bowel syndrome, predicting response (biomarkers)

1 | INTRODUCTION

Dietary therapies are increasingly used for treatment of functional bowel disorders (FBD).[1] Between 60% and 89% of patients with FBD believe that food exacerbate symptoms and consequently modify their diet.[2-4] The use of diet as therapy has been driven from two directions; one by public interest and the other by increased scientific knowledge of the role of diet in altering gastrointestinal symptoms. New technology and research advances have shown diet effects can be dependent on the microbiome and can also modify the microbiota profile, both of which has been implicated in the etiology of these disorders.[5,6] Interest in using diet as therapy has sparked an expansion in types of dietary therapies available with varying levels of supporting evidence and different concepts for mechanism of action.

The pathophysiology of irritable bowel syndrome (IBS) is unclear and thought to be caused by a multitude of factors including changes in gastrointestinal motility,[7,8] visceral hypersensitivity,[9,10] dysregulation of the brain-gut axis,[11] low-grade inflammation,[12-14] alterations to the microbiota,[15,16] among others. With the growing evidence that diet can be effective in IBS patients, it is now also being targeted to patients with quiescent inflammatory bowel disease (IBD) to treat co-existing IBS symptoms. It is estimated that 35%-45% of patients with IBD will have symptoms of IBS during remission.[17,18] However, dietary therapies are not well studied in this patient group.

Despite the widespread use of these diets, there are still many unanswered questions regarding the role of diet in FBD. In particular, which of the many diet types should be used and in which patients; how can doctors, dietitians, or other health care workers predict which patient will respond to which type of therapy; are dietary therapies safe; how long should the diet be use for; and what level of restriction is necessary? This review aims to explore these questions with a focus on diets designed to assist in reducing functional symptoms in IBS and quiescent IBD.

Underlying reasons for symptoms

Evidence that identification of underlying reasons for IBS-symptoms can improve patient care is provided by a clinical retrospective study that found **98% of 303 patients with diarrhoea-predominant IBS (IBS-D) and functional diarrhoea had an alternative explanation for their symptoms**, including bile acid induced diarrhoea, carbohydrate intolerance, gluten enteropathy and non-celiac gluten intolerance, and responded very well to treatments that corresponded with their new diagnosis.

Med Hypotheses. 2011 Jan;76(1):97-9.

Medical Hypotheses 76 (2011) 97–99

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Diarrhea Predominant Irritable Bowel Syndrome (IBS-D): Fact or fiction

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ARTICLE INFO

Article history:
Received 6 April 2010
Accepted 14 August 2010

SUMMARY

Diarrhea Predominant Irritable Bowel Syndrome IBS (IBS-D) and functional diarrhea constitute 50% of cases treated by gastroenterology specialists and a significant proportion of those treated in a primary physicians practice. The size of the problem and the difficulty in successfully addressing these entities has frustrated patients and physicians alike.

The presented data delineates work-up, final diagnoses and clinical outcomes in the largest single clinical retrospective study of 303 patients with an initial presentation of IBS-D and functional diarrhea. Results indicate that 298 (98%) patients were found to have a diagnosis different from the initial presentation of IBS-D, and 204 (68%) of the patients studied had conditions related to treatable bile acid abnormalities.

After identifying these clinical diagnoses and instituting appropriate therapy, 98% of these patients had a favorable response, as measured by a decrease in the number of bowel movements to less than three per day and a significant change in the consistency of the stools. This finding is dramatically different from the poor response generally experienced from conventional therapy for IBS-D and functional chronic diarrhea. The data presented in this study substantiates the hypothesis that IBS-D and functional diarrhea do not exist as true clinical entities and explains the previous lack of satisfactory therapeutic response.

Symptoms experienced by these patients were caused by a collection of different clinical conditions bunched up under this "umbrella" diagnosis of IBS-D. Once these separate entities were identified and appropriately addressed, the clinical response was quite impressive and encouraging. The implication of this hypothesis could be of vital importance because of the number of those suffering from these symptoms.

Introduction

Criteria and diagnostic work-up for irritable bowel syndrome (IBS) has evolved through many phases in search of defining an entity that affects up to 15% of the population in the United States [1–3]. The opacity of the etiology has lead to far reaching explanations for such entities, none of which has been satisfactory. This study was initiated to analyze 303 patients, frequently seen by more than one physician, diagnosed with chronic diarrhea and presented to this gastroenterologist practice as "diarrhea predominant IBS".

Symptoms at the time of initial presentation satisfied the established Rome criteria for irritable bowel syndrome [4]. Although pain is fundamental in the diagnosis of IBS, abdominal discomfort and pain may be difficult to differentiate by patients and physicians. As a result, differentiating true IBS-D from functional diarrhea is difficult, and physicians frequently lump chronic diarrhea with negative work-up as "diarrhea predominant-IBS". Many feel that Manning/Rome criteria are too restrictive [5–7].

The patients in this study presented with more than three bowel movements per day for a minimum of 2 months associated with urgency, and at times, incontinence. All shared a common characteristic of "bathroom mapping" which is the anxious search for a bathroom in all venues.

Analysis of the data in this study was revealing. The favorable response, as defined by less than three bowel movements per day, lead to a different fundamental understanding and approach to patients with chronic diarrhea and supports the proposed hypothesis.

Hypothesis

This hypothesis contends that Diarrhea Predominant Irritable Bowel Syndrome (IBS-D) and functional diarrhea are not true clinical entities as previously thought, but a collection of different, separate medical conditions. Once these conditions are identified and appropriately addressed, the clinical response is very impressive

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0306-9877/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.mehy.2010.08.040

Biomarker-led investigation

A retrospective analysis of a biomarker test that identifies potentially treatable underlying causes of IBS in people that meet Rome III criteria and found that **up to 94% have results suggesting a treatable underlying diagnosis or functional problem.**

Glob Adv Health Med. 2014 May;3(3):9-15.

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IMPROVING HEALTHCARE OUTCOMES WORLDWIDE

ORIGINAL RESEARCH

Frequency of Abnormal Fecal Biomarkers in Irritable Bowel Syndrome

Julius Goepp, MD, *United States*; Elizabeth Fowler, PhD, *United States*; Teresa McBride, ND, *United States*; Darryl Landis, MD, *United States*

ABSTRACT

Primary Study Objective: Determine the frequency of abnormal fecal biomarker test results in patients with 13 irritable bowel syndrome (IBS)–related ICD-9 (International Statistical Classification of Diseases and Related Health Problems) codes.

Study Design: Quantitative review of de-identified records from patients in whom IBS was a possible diagnosis.

Methods: Records were selected for analysis if they included any of 13 IBS-related diagnostic codes and laboratory test results of fecal testing for all biomarkers of interest. Data collection was restricted to one 12-month period. Frequency distributions were calculated to identify rates of abnormal results for each biomarker within the total number of tests conducted in the eligible population.

Results: Two thousand, two hundred fifty-six records were included in the study, of which 1867 (82.8%) included at least one abnormal value. Quantitative stool culture for beneficial bacteria (*Lactobacillus* and *Bifidobacterium*) indicated low growth suggestive of intestinal dysbiosis in 73.1% of records, followed by abnormally elevated eosinophil protein X (suggestive of food allergy) in 14.3%, elevated calprotectin (suggestive of inflammation) in 12.1%, detection of parasites in 7.5%, and low pancreatic elastase (suggestive of exocrine pancreatic insufficiency) in 7.1%.

Conclusions: Abnormal fecal biomarkers are prevalent in patients with diagnoses suggestive of IBS. Abnormal fecal biomarker testing, if confirmed in additional independent clinical trials, could substantially reduce the economic costs associated with diagnosis and management of IBS.

BACKGROUND

It is estimated that 10% to 20% of Americans in their most productive years are afflicted with irritable bowel syndrome (IBS).[1-3] IBS imposes a social burden estimated to cost approximately $20 billion a year.[4]

Despite the existence of guidelines to the contrary, many primary care physicians continue to view IBS as a "diagnosis of exclusion" and pursue costly and often invasive diagnostic studies.[5-7] The conditions to be excluded (such as inflammatory bowel disease, malignancy, and infectious colitis), while carrying potentially grave prognoses, are rarely discovered during evaluation of patients who have IBS or other functional bowel disorders.[5,8-10]

Conversely, evidence is emerging that the syndromic symptoms that define IBS according to the Rome III clinical criteria (recurrent abdominal pain or discomfort, improvement with defecation, change in frequency or in form/appearance of stool) may in fact have protean causes, often arising from one or more specific gastrointestinal (GI) conditions.[11] The advent of relatively inexpensive tests based on identification of selected fecal biomarkers now makes it possible to identify or exclude several of these underlying conditions, with the potential for a positive clinical and economic impact.[12]

GI conditions capable of producing manifestations of IBS include exocrine pancreatic insufficiency, which has an estimated prevalence of 6.1% in subjects with IBS symptomatology, and may be suggested by low levels of fecal pancreatic elastase (PE).[13] Inflammatory disorders such as inflammatory bowel disease may be discriminated from IBS with the use of the neutrophil-derived protein calprotectin in stool.[14-17] Food allergies, which have a reported prevalence rate of about 25% in IBS patients,[18] may be suggested by the presence of elevated fecal levels of eosinophil protein X, which may also be elevated in inflammatory bowel disorders and parasitic infections.[19-25] Pathogenic infections such as *Clostridium difficile* and parasites such as *Giardia lamblia* are reported in 5.7% and 6.5%, respectively, of people with symptoms attributable to IBS[26,27] and are readily detected on fecal specimens using established techniques such as culture and light microscopy. *Blastocystis hominis*, the most common human intestinal parasite, was long thought to be non-pathogenic.[28,29] Some (but not all) recent studies, however, have demonstrated a significant increased prevalence of *Blastocystis hominis* in IBS patients compared with controls, and at least one authority has recommended treatment with metronidazole in the face of a positive identification of the organism and a symptomatic patient.[29-35]

Even in the absence of known pathogens, close study of the microbiome reveals differences in fecal bacterial populations (dysbiosis) between IBS patients and healthy controls. While a clear-cut "IBS microbiotype" has not been identified, studies have described relative increases in detrimental groups of commensal bacteria and decreases in beneficial groups, most specifically a decrease in Bifidobacteria and an increase in

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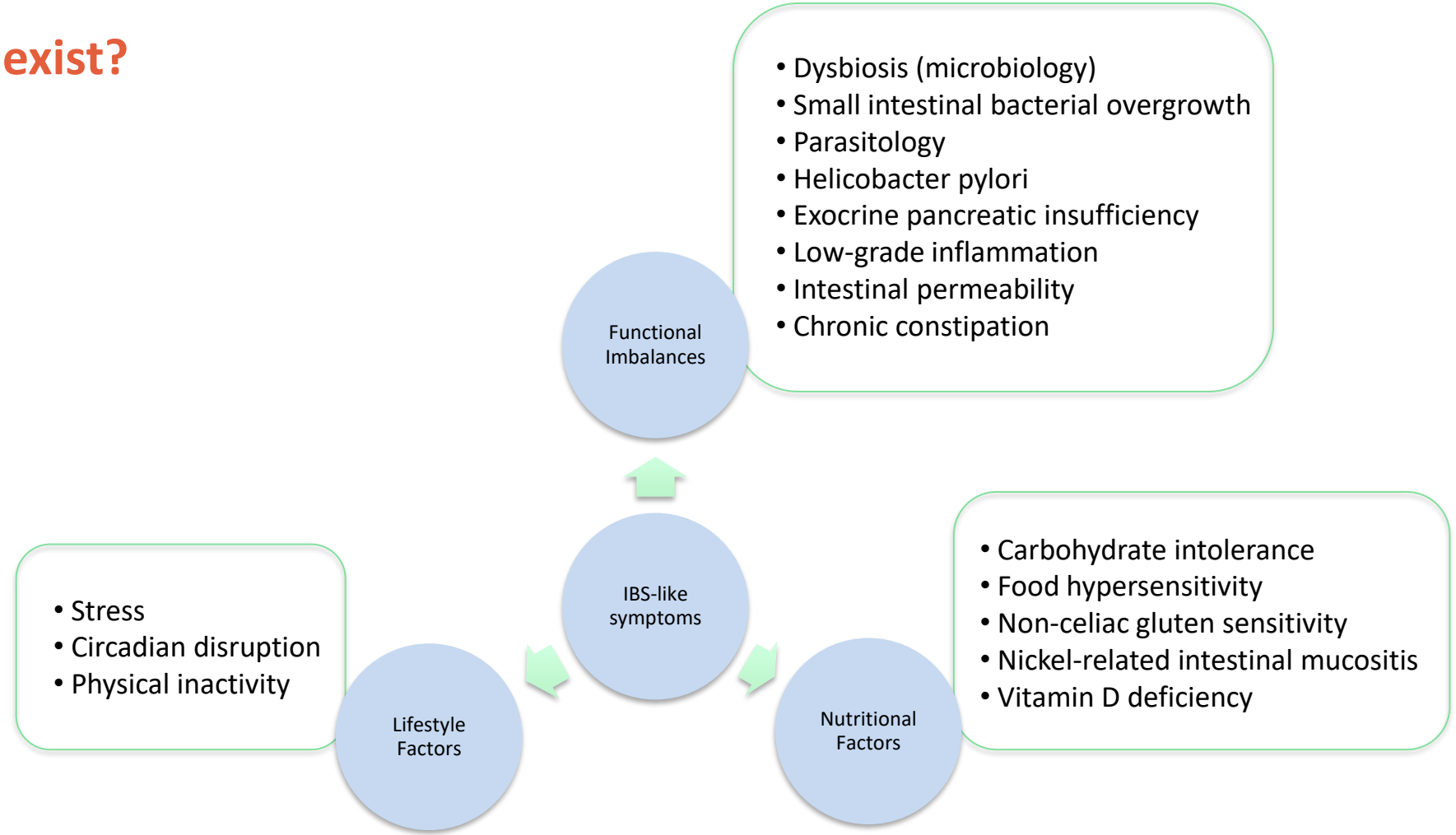
Citation
Global Adv Health Med. 2014;3(3):9-15. DOI: 10.7453/gahmj.2013.099

Key Words
Fecal biomarkers, irritable bowel syndrome (IBS), microbiome, eosinophilic protein X, calprotectin, stool culture, pancreatic elastase

Funding Source
Genova Diagnostics, Inc, Asheville, North Carolina

Disclosures
Drs Fowler, Hanaway, Landis, and McBride disclosed that they are employed by Genova Diagnostics, Inc.
Dr Landis owns stock in Genova Diagnostics.
Dr Goepp received consultant's fees from Genova Diagnostics, Inc.

Does IBS exist?

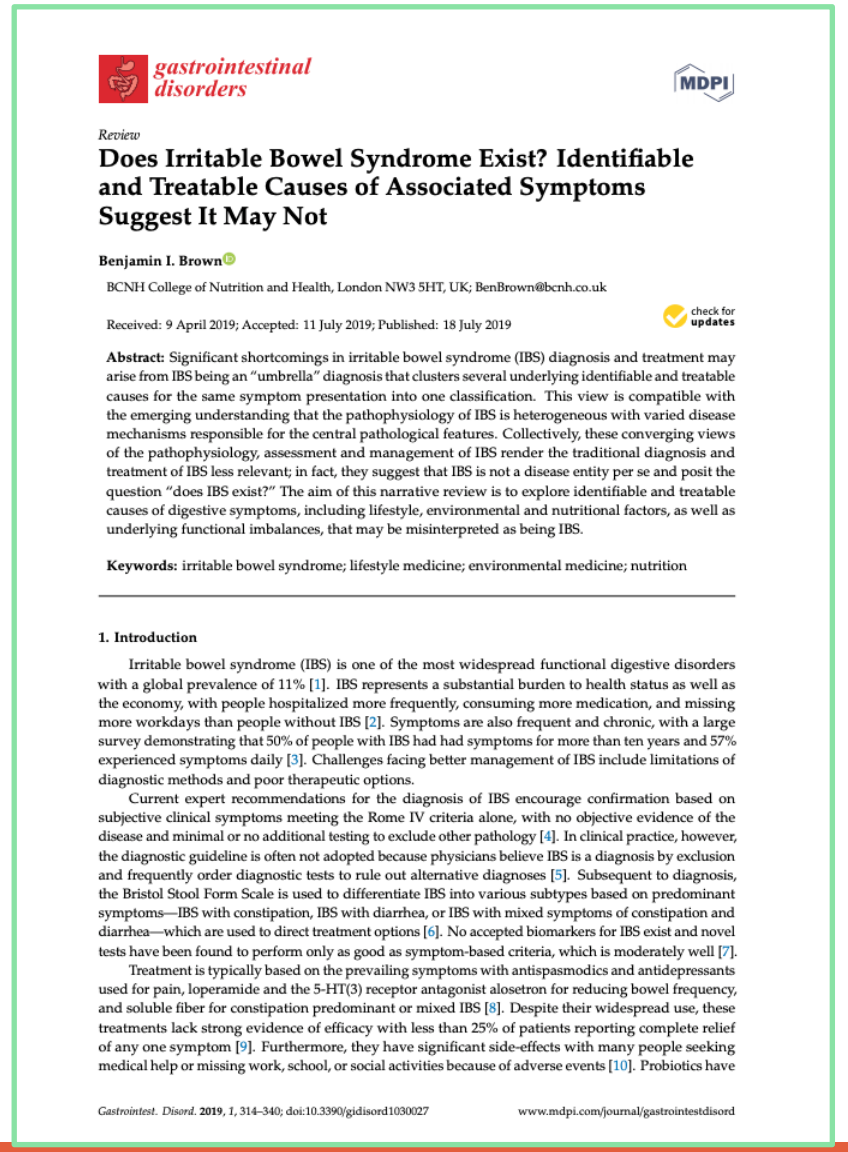


Brown, B.I. Does Irritable Bowel Syndrome Exist? Identifiable and Treatable Causes of Associated Symptoms Suggest It May Not. *Gastrointest. Disord.* 2019, *1*, 314-340.

Clinical management needs to get personal

"Obtaining a better understanding of each patient's pathophysiology with clinical and molecular assessments could therefore help improve diagnosis and target different therapies to individuals most likely to benefit."

Gastrointest. Disord. 2019, *1*, 314-340.



gastrointestinal disorders

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Review

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Keywords: irritable bowel syndrome; lifestyle medicine; environmental medicine; nutrition

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Current expert recommendations for the diagnosis of IBS encourage confirmation based on subjective clinical symptoms meeting the Rome IV criteria alone, with no objective evidence of the disease and minimal or no additional testing to exclude other pathology [4]. In clinical practice, however, the diagnostic guideline is often not adopted because physicians believe IBS is a diagnosis by exclusion and frequently order diagnostic tests to rule out alternative diagnoses [5]. Subsequent to diagnosis, the Bristol Stool Form Scale is used to differentiate IBS into various subtypes based on predominant symptoms—IBS with constipation, IBS with diarrhea, or IBS with mixed symptoms of constipation and diarrhea—which are used to direct treatment options [6]. No accepted biomarkers for IBS exist and novel tests have been found to perform only as good as symptom-based criteria, which is moderately well [7].

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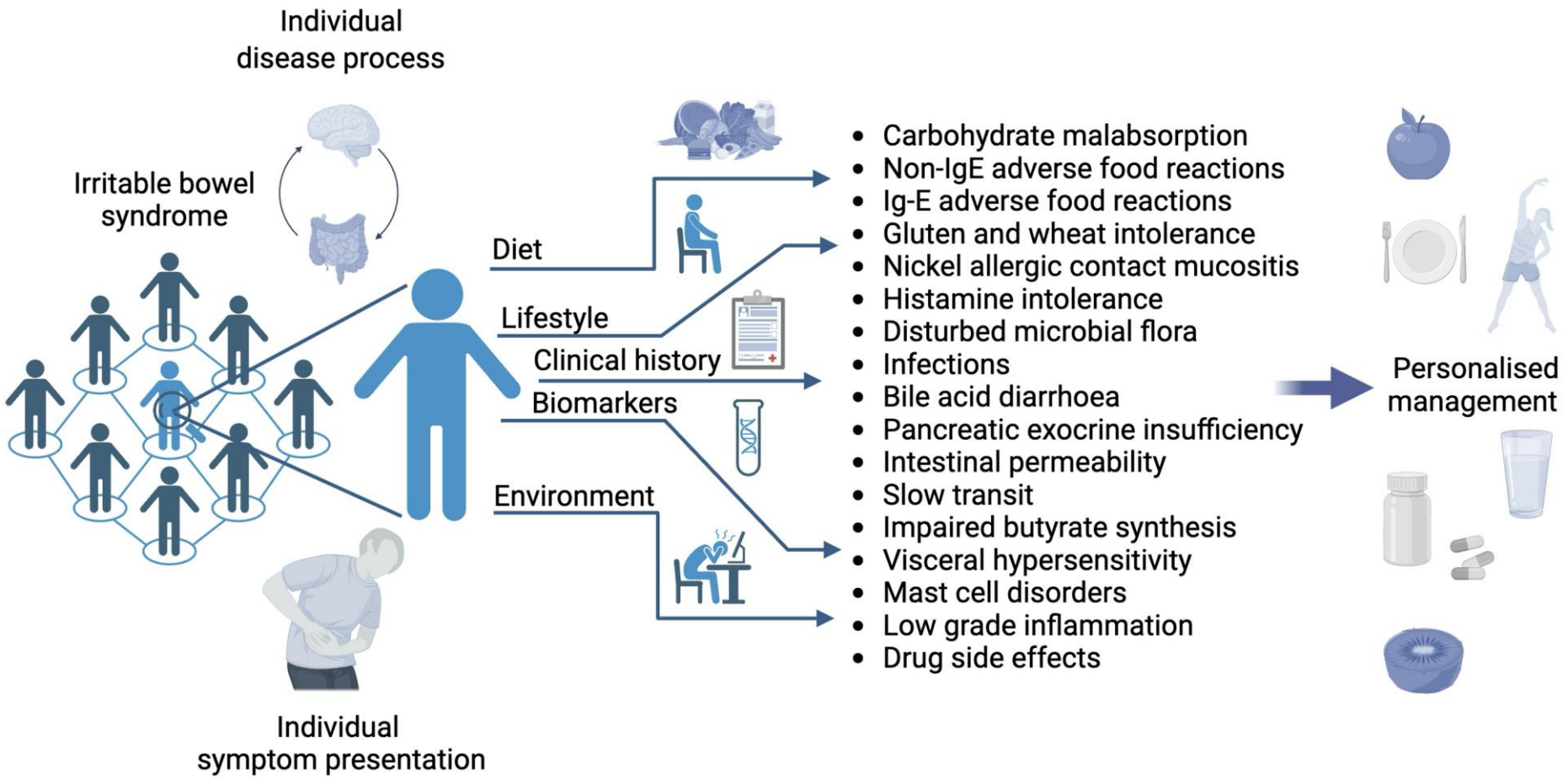
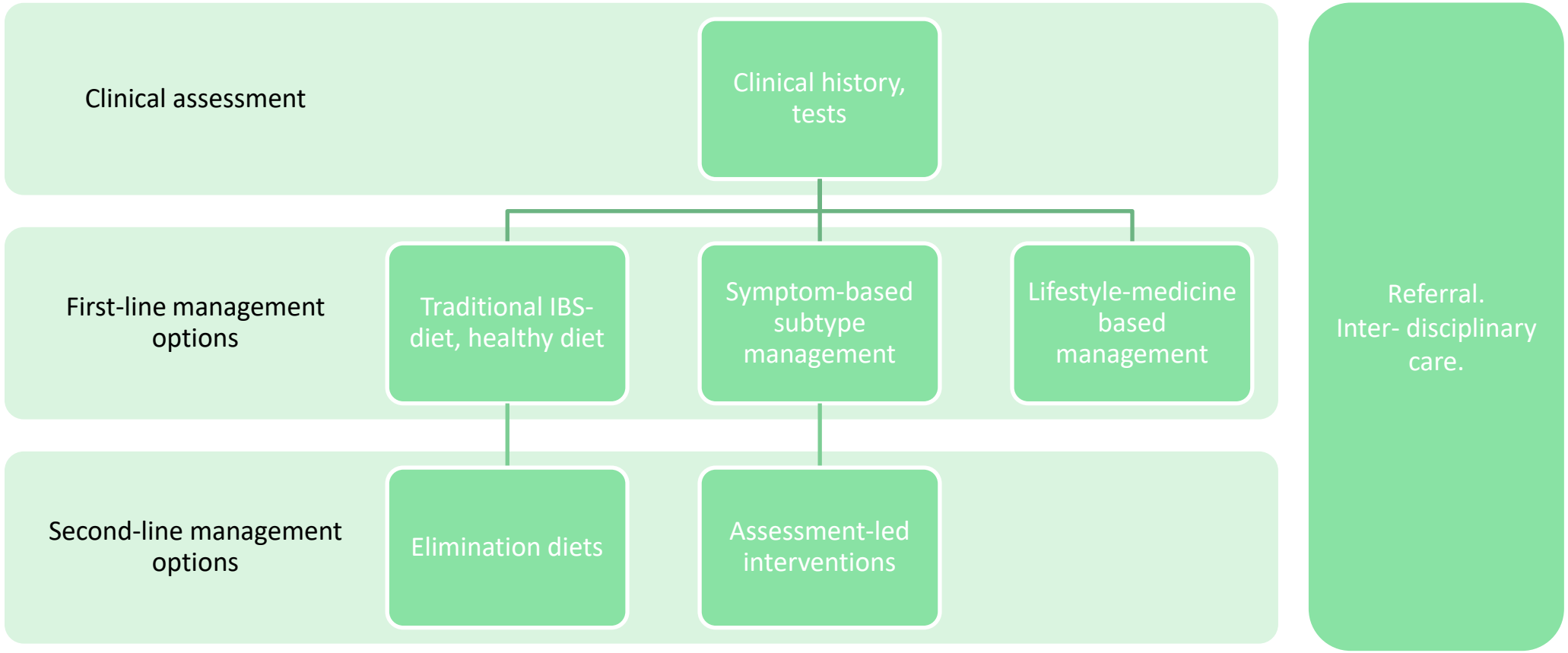
Contributory factors that may explain an individual's IBS-like symptoms



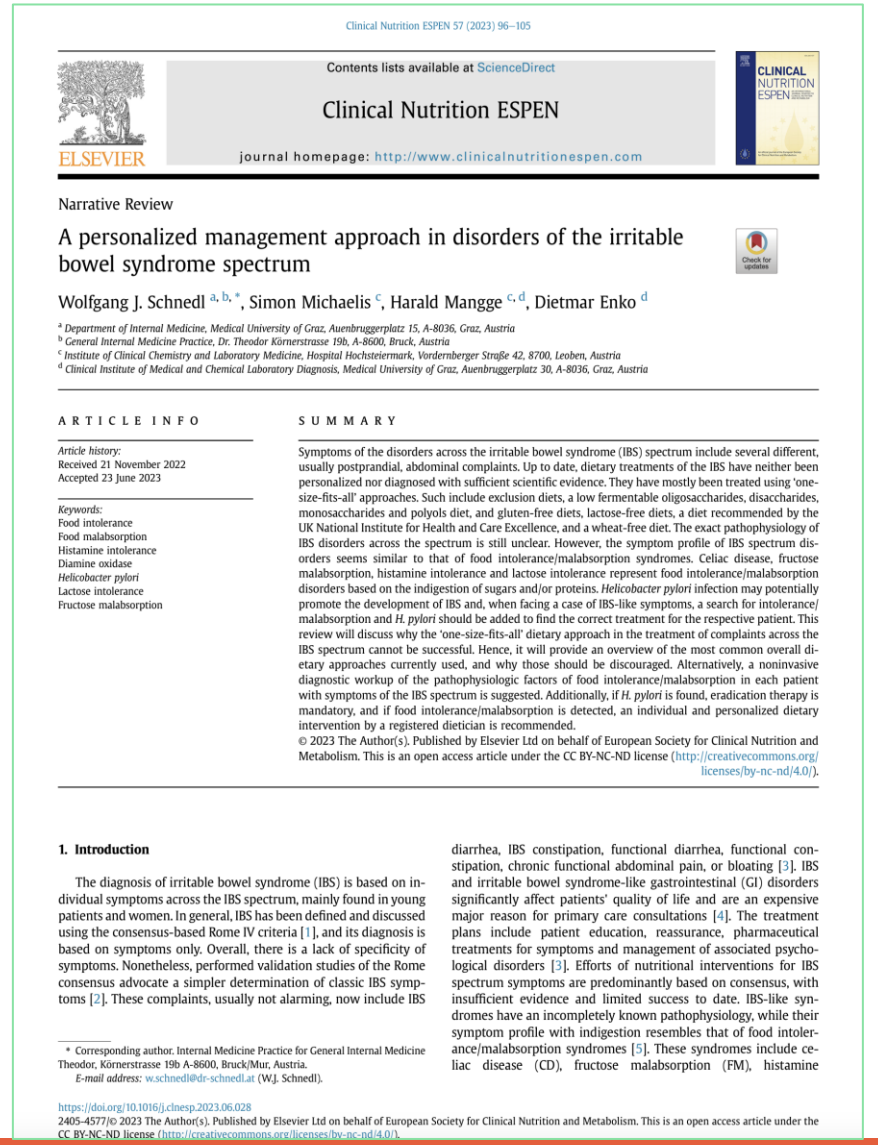
How do we approach a complex problem?



Can we personalize diet?

"Symptoms of the disorders across the irritable bowel syndrome (IBS) spectrum include several different, usually postprandial, abdominal complaints. **Up to date, dietary treatments of the IBS have neither been personalized nor diagnosed with sufficient scientific evidence.** They have mostly been treated using 'one-size-fits-all' approaches."

Clin Nutr ESPEN. 2023 Oct;57:96-105.



Clinical Nutrition ESPEN 57 (2023) 96–105

Contents lists available at ScienceDirect

Clinical Nutrition ESPEN

journal homepage: http://www.clinicalnutritionespen.com

Narrative Review

A personalized management approach in disorders of the irritable bowel syndrome spectrum

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ARTICLE INFO

Article history:
Received 21 November 2022
Accepted 23 June 2023

Keywords:
Food intolerance
Food malabsorption
Histamine intolerance
Diamine oxidase
Helicobacter pylori
Lactose intolerance
Fructose malabsorption

SUMMARY

Symptoms of the disorders across the irritable bowel syndrome (IBS) spectrum include several different, usually postprandial, abdominal complaints. Up to date, dietary treatments of the IBS have neither been personalized nor diagnosed with sufficient scientific evidence. They have mostly been treated using 'one-size-fits-all' approaches. Such include exclusion diets, a low fermentable oligosaccharides, disaccharides, monosaccharides and polyols diet, and gluten-free diets, lactose-free diets, a diet recommended by the UK National Institute for Health and Care Excellence, and a wheat-free diet. The exact pathophysiology of IBS disorders across the spectrum is still unclear. However, the symptom profile of IBS spectrum disorders seems similar to that of food intolerance/malabsorption syndromes. Celiac disease, fructose malabsorption, histamine intolerance and lactose intolerance represent food intolerance/malabsorption disorders based on the indigestion of sugars and/or proteins. *Helicobacter pylori* infection may potentially promote the development of IBS and, when facing a case of IBS-like symptoms, a search for intolerance/malabsorption and *H. pylori* should be added to find the correct treatment for the respective patient. This review will discuss why the 'one-size-fits-all' dietary approach in the treatment of complaints across the IBS spectrum cannot be successful. Hence, it will provide an overview of the most common overall dietary approaches currently used, and why those should be discouraged. Alternatively, a noninvasive diagnostic workup of the pathophysiologic factors of food intolerance/malabsorption in each patient with symptoms of the IBS spectrum is suggested. Additionally, if *H. pylori* is found, eradication therapy is mandatory, and if food intolerance/malabsorption is detected, an individual and personalized dietary intervention by a registered dietician is recommended.

1. Introduction

The diagnosis of irritable bowel syndrome (IBS) is based on individual symptoms across the IBS spectrum, mainly found in young patients and women. In general, IBS has been defined and discussed using the consensus-based Rome IV criteria [1], and its diagnosis is based on symptoms only. Overall, there is a lack of specificity of symptoms. Nonetheless, performed validation studies of the Rome consensus advocate a simpler determination of classic IBS symptoms [2]. These complaints, usually not alarming, now include IBS diarrhea, IBS constipation, functional diarrhea, functional constipation, chronic functional abdominal pain, or bloating [3]. IBS and irritable bowel syndrome-like gastrointestinal (GI) disorders significantly affect patients' quality of life and are an expensive major reason for primary care consultations [4]. The treatment plans include patient education, reassurance, pharmaceutical treatments for symptoms and management of associated psychological disorders [3]. Efforts of nutritional interventions for IBS spectrum symptoms are predominantly based on consensus, with insufficient evidence and limited success to date. IBS-like syndromes have an incompletely known pathophysiology, while their symptom profile with indigestion resembles that of food intolerance/malabsorption syndromes [5]. These syndromes include celiac disease (CD), fructose malabsorption (FM), histamine

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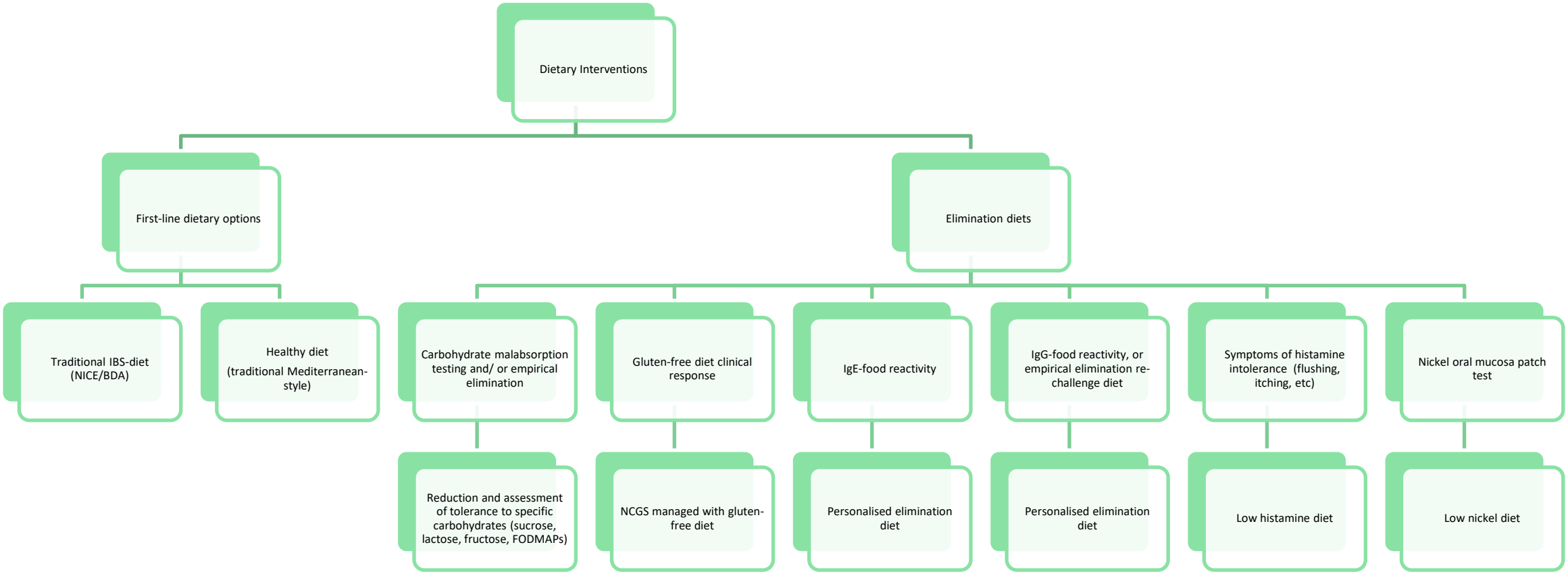
https://doi.org/10.1016/j.clnesp.2023.06.028
2405-4577/

Dietary interventions for IBS-like symptoms



Diet example 1: sucrase-isomaltase deficiency

"The classic congenital sucrase-isomaltase deficiency (CSID) manifests itself during infancy when one begins to introduce fruits and juices into the diet and leads to severe diarrhoea, poor weight gain, irritability, and diaper rash. The treatment mainly consists of avoiding starch and sucrose, which reverses the symptoms. **Milder forms of mutations can present clinically later in life** with the same symptoms as in other carbohydrate intolerances, especially diarrhoea, **and can be misdiagnosed as IBS** in adults."

Mol Med Rep. 2021 Oct;24(4):732.

MOLECULAR MEDICINE REPORTS 24: 732, 2021

Theories behind the effect of starch- and sucrose-reduced diets on gastrointestinal symptoms in irritable bowel syndrome (Review)

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Received July 1, 2021; Accepted July 22, 2021

DOI: 10.3892/mmr.2021.12372

Abstract. Increased amounts of starch and sugar have been added to the diet in the Western world during the last decades. Undigested carbohydrates lead to bacterial fermentation and gas production with diffusion of water, causing abdominal bloating, pain and diarrhea. Therefore, dietary advice is the first line of treatment of irritable bowel syndrome (IBS), a disease characterized by abdominal pain and altered bowel habits without any organic findings. Recently, a diet with a reduction of starch and sucrose led to a marked effect on gastrointestinal (GI) symptoms. The mechanism is unknown, but three possible mechanisms are presented in the present review. First, functional variants of the enzyme sucrase-isomaltase (SI) have been described in IBS. A subgroup of patients with IBS may thus suffer from partial SI deficiency with reduced digestion of starch and sucrose. Second, fructose absorption is less efficient than glucose absorption, which may lead to a physiological fructose malabsorption when ingesting high amounts of sucrose. A third mechanism is that high-sugar diets causing hyperglycemia, hyperinsulinemia and weight gain have led to painful neuropathy in animal models; whereas, improved metabolic control in humans has led to improvement of neuropathy. Starch- and sucrose-reduced diets lead to decreased levels of C-peptide, insulin, gastric inhibitory peptide, leptin and weight reduction. These metabolic changes may reduce the excitability of the hypersensitive nervous system often found in IBS and, thereby, lead to the reduced symptoms found after the diet. In conclusion, further studies are needed to investigate the pathophysiology behind development of symptoms after starch and sucrose intake, and the mechanisms behind symptom relief after reduced intake.

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Key words: fructose malabsorption, neuropathy, starch, sucrose, sucrase-isomaltase deficiency

Contents

1. Introduction

Gastrointestinal (GI) symptoms without any organic changes are called functional gastrointestinal disorders (FGID). The most common of these disorders is irritable bowel syndrome (IBS) (1). The pathophysiology behind FGID is unknown, but visceral hypersensitivity, psychological factors, low-grade inflammation, alterations in gut microbiota composition, or hormonal profile have been discussed (2).

IBS symptoms are frequently experienced during food intake, and as such, dietary interventions are usually prescribed to improve the symptoms (3). Also, patients with IBS have been found to have altered expression of endocrine cells in the GI tract and different levels of circulating hormones (4-6).

Dietary changes may influence the production of gut hormones since the production is predominantly influenced by food ingestion and food nutrient content (7). Hormones such as C-peptide, gastric inhibitory peptide (GIP), glucagon, glucagon-like peptide-1 (GLP-1), and insulin are key hormones in regulation of glucose homeostasis. These hormones control energy and glucose metabolism by acting on the function of the digestive system in glucose regulation, motility, and pancreatic function (8,9). Leptin controls appetite and food intake, thereby regulating energy intake (10). Thus, the improvement of IBS symptoms with dietary changes may possibly be linked to the effect of changes in gut hormones (11).

The first line of dietary advice is the National Institute for Health and Care Excellence (NICE) guidelines, which recommend regular meal patterns and decreased intake of mineral water, caffeine, fat, and spicy foods (12), or the low FODMAP diet, which advocates exclusion of fermentable oligo-, di- and monosaccharides and polyols (13). These diets have an effect in 20-50% of IBS patients (14).

Diet example 1: sucrase-isomaltase deficiency

Diet	Diet description	Evidence for efficacy	Biomarkers	Biomarker evidence
Low sucrose diet	Modified dietary guidelines for patients with congenital sucrase-isomaltase deficiency including avoiding sucrose containing foods, foods with added sugars, and replacing refined grain product with high fiber alternatives.	Low sucrose diets have been shown to reduce symptoms. Congenital sucrase-isomaltase deficiency may also masquerade as adult IBS and respond to diet.	Sucrase-isomaltase gene variants	Predict a moderately better response to a low sucrose diet in IBS-D. May predict poor response to a LFD. Negative test does not rule out congenital deficiency as not all gene variants have been identified.

Diet example 2: histamine intolerance

"…histamine and, histamine intolerance, should be considered in differential diagnoses of patients with functional, nonspecific, non-allergic gastrointestinal complaints."

Crit Rev Food Sci Nutr. 2021;61(17):2960-2967.

CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
https://doi.org/10.1080/10408398.2020.1791049

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REVIEW

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Considering histamine in functional gastrointestinal disorders

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ABSTRACT

In westernized countries, adverse reactions to ingested foods are reported to affect up to 20% of the population. Functional, nonspecific, non-allergic gastrointestinal complaints are mainly due to the intolerance/malabsorption of carbohydrates (lactose and fructose), proteins (gluten), and biogenic amines (histamine). Food intolerance/malabsorption is defined by one or several of the above mentioned food components not being degraded and/or absorbed properly within the gastrointestinal tract. Food intolerance/malabsorption causes variable, functional, nonspecific, non-allergic gastrointestinal and extra-intestinal complaints, and a detailed diagnostic workup for all possible etiologic factors in individual patients is essential. Usually, evaluation for histamine intolerance is not included in differential diagnoses of patients with functional, nonspecific, non-allergic gastrointestinal complaints. A targeted dietary intervention for single or possibly combined intolerance/malabsorption is required. In this article, we review currently discussed differential diagnoses and available tests for intolerance/malabsorption. Accordingly, we aim to outline why including histamine and, histamine intolerance, should be considered in differential diagnoses of patients with functional, nonspecific, non-allergic gastrointestinal complaints.

KEYWORDS

Histamine; lactose; fructose; diamine oxidase; food intolerance; food malabsorption; mastozytosis

Introduction

Adverse reactions to ingested foods causing functional, nonspecific, non-allergic gastrointestinal complaints are due to the intolerance/malabsorption of carbohydrates (lactose and fructose), proteins (gluten), and biogenic amines (histamine). However, there is a lack of understanding of these functional, nonspecific, non-allergic symptoms and diagnoses are limited by the lack of accepted standardized tests for the underlying mechanisms (Talley 2020). Due to these disorders being increasingly discussed in the media, a growing number of people change their diets. Nevertheless, intolerance/malabsorption is causing variable gastrointestinal (GI) and extra-intestinal complaints (Mitchell et al. 2019). Generally, symptoms are observed subjectively, and intolerance/malabsorption-caused symptoms are not dependably confirmed by medical tests. Scientific evidence to support this postulated link is increasing, but reliable comprehensive evaluations and/or laboratory tests for definite diagnoses are still needed (Reese et al. 2017).

Food intolerance/malabsorption requires detailed diagnostic examination with available tests for all possible etiologic aspects of each individual patient and, subsequently, personalized treatment with individual dietary plans. Only the targeted dietary intervention for each single, or possibly combined, intolerance/malabsorption may help to provide sustained relief (Enko et al. 2016). Here we review currently discussed differential diagnoses and available tests, and outline why including histamine intolerance (HIT) in the differential diagnoses of intolerance/malabsorption should be considered for patients with functional, nonspecific, non-allergic GI and extra-intestinal complaints.

Food intolerance and malabsorption

There is growing public interest in food intolerance/malabsorption for people who experience reactions to food. Food intolerance/malabsorption causes functional, nonspecific, non-allergic GI complaints and extra-intestinal symptoms. In westernized countries, adverse reactions that may influence and impair digestion are reported to affect up to 20% of the population (Mitchell et al. 2019).

Recent investigations have led to an improved understanding of food components, particularly of sugars (lactose and fructose), proteins (gluten), and biogenic amines (including histamine). In most cases of intolerance/malabsorption one or a combination of the above described food components cannot be degraded and/or absorbed properly within the GI tract. GI bacteria then use various catabolic enzymes to degrade and ferment ingested food. However, experiments suggest that the quantity, type and composition of dietary carbohydrates and proteins change the metabolic output of these microbes (Schink et al. 2018; Albenberg and Wu 2014).

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Diet example 2: histamine intolerance

Diet	Diet description	Evidence for efficacy	Biomarkers	Biomarker evidence
Histamine diet	Recommendations vary but most often include restriction of cured and semi cured cheese, grated cheese, oily fish, canned and semi preserved oily fish derivatives, dry-fermented meat products, spinach, tomatoes, fermented cabbage, strawberries, citrus, wine, and beer.	Histamine intolerance has been suggested in a subgroup of IBS patients. A histamine diet has been shown to symptoms in patients presenting primarily with functional abdominal symptoms. This is supported by benefit of DOA enzyme intervention on GI symptoms. FODMAPs may favour the production of faecal histamine by Klebsiella aerogenes in a subgroup of IBS patients. A moderate correlation was found between visceral pain severity and urinary histamine with an LFD.	Serum DAO	Does not have reliable diagnostic value. Despite uncertainty, may be useful to complement diagnosis and prediction of clinical response to treatment.
			Urinary histamine	Methylhistamine in urine is emerging as a potential biomarker.
			DAO gene variants	The relevance of gene variants to histamine intolerance is unknown. DAO gene variants were associated with lower serum DAO in a subgroup of people with histamine intolerance, but not with clinical histamine intolerance phenotype.

Can biomarkers guide management?

"Multiple mechanisms are implicated in the complex pathophysiology of IBS. Many recent studies have focused on the identification of specific biomarkers that would aid in the diagnosis and identification of subgroups, and lead to more specific treatments for IBS; however, none have been shown to accurately identify all patients with IBS, but rather specific subgroups of IBS. This is **because IBS is heterogeneous and not simply one disease. In the future, IBS symptoms will be known to have different causes as identified by different biomarkers.** Targeted therapies for these subgroups will then be possible and effective."

Expert Rev Gastroenterol Hepatol. 2017 Apr;11(4):303-316.

EXPERT REVIEW OF GASTROENTEROLOGY & HEPATOLOGY, 2017
VOL. 11, NO. 4, 303–316
http://dx.doi.org/10.1080/17474124.2017.1288096

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REVIEW

Biomarkers as a diagnostic tool for irritable bowel syndrome: where are we?

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ABSTRACT

Introduction: Irritable bowel syndrome (IBS) is a common condition in clinical practice. There are currently no objective tests to rule in the disease, but rather tests to rule out other diseases. Biomarkers in IBS may provide the tools needed for diagnosis, prognosis and therapy. These include identification of differences in microbial composition, immune activation, bile acid composition, colonic transit, and alteration in sensation in subgroups of IBS patients.
Areas covered: Studies included in our review were chosen based on a PubMed search for 'biomarkers' and 'IBS'. We have reviewed the literature on biomarkers to appraise their accuracy, validity and whether they are actionable. We have not covered genetic associations as biomarkers in this review.
Expert commentary: There is significant promise in the usefulness of biomarkers for IBS. The most promising actionable biomarkers are markers of changes in bile acid balance, such as elevated bile acid in the stool, and altered colonic transit. However, there is also potential for microbial studies and mucosal proteases as future actionable biomarkers.

ARTICLE HISTORY
Received 11 November 2016
Accepted 25 January 2017

KEYWORDS
Bile acid; chromogranin; enterochromaffin cells; irritable bowel syndrome; lymphocytes; mast cells; microbiome; proteases; scintigraphic transit; visceral sensation

1. Introduction

1.1. Overview of diagnosis, burden, and mechanisms of irritable bowel syndrome (IBS)

The diagnosis of IBS is traditionally based on the symptoms of recurrent abdominal pain associated with diarrhea (IBS-D), constipation (IBS-C), or both (IBS-M) [1]. Ideally, the diagnosis of IBS should rely on the clinical history, while avoiding invasive and expensive tests. However, this diagnosis may involve multiple clinic and emergency room visits, extensive investigations including blood and fecal testing, and multiple radiographic and endoscopic studies to exclude inflammatory bowel diseases (IBD), celiac disease, and gastrointestinal infections.

There is a significant burden of illness in IBS, associated with high healthcare use and cost [2], while accurate, safe and cost-effective diagnostic tools are still not widely available.

Multiple mechanisms are implicated in the complex pathophysiology of IBS [3]. Many recent studies have focused on the identification of specific biomarkers that would aid in the diagnosis and identification of subgroups, and lead to more specific treatments for IBS [4]; however, none have been shown to accurately identify all patients with IBS, but rather specific subgroups of IBS. This is because IBS is heterogeneous and not simply one disease. In the future, IBS symptoms will be known to have different causes as identified by different biomarkers. Targeted therapies for these subgroups will then be possible and effective.

Continued research in the quest to identify clinically significant biomarkers, based on distinct pathophysiological mechanisms, should lead to more specific, targeted therapy for subgroups of IBS patients.

IBS is a heterogeneous disease; indeed, this same phenotype, characterized by a symptom complex with different etiological mechanisms, may defy identification of a single biomarker, and we anticipate that, in the future, some subgroups of patients now included in IBS will likely be specifically identified, diagnosed as a separate disease, and removed from the umbrella term of 'IBS'. Examples include bile acid diarrhea and constipation associated with rectal evacuation disorders, which are currently included under IBS-D and IBS-C respectively.

Certainly, for all the biomarkers proposed, sensitivity and specificity are not available for all data and replication is needed before their widespread use. As we reviewed the biomarkers, we assessed their availability and current cost-effectiveness in accordance with the guidance of Barbara [4]. Availability in different clinical settings was categorized as widely available ('high' availability), available only in specialized clinics ('moderate' availability), and only available in referral labs/centers ('low' availability). Cost-effectiveness was based on cost of the biomarker test and its actionable potential, and was categorized as high, moderate or low.

Certain genetic factors in IBS can potentially predispose to the development of IBS, as reviewed elsewhere [5]; however, their potential roles in the management (diagnosis or treatment) of IBS are not definitely proven and, therefore, they will not be considered further in this review.

1.2. Definition of biomarkers

Biomarkers are molecular, histologic, radiographic or physiologic characteristics that indicate a normal biological or pathogenic process or responses to therapeutic intervention

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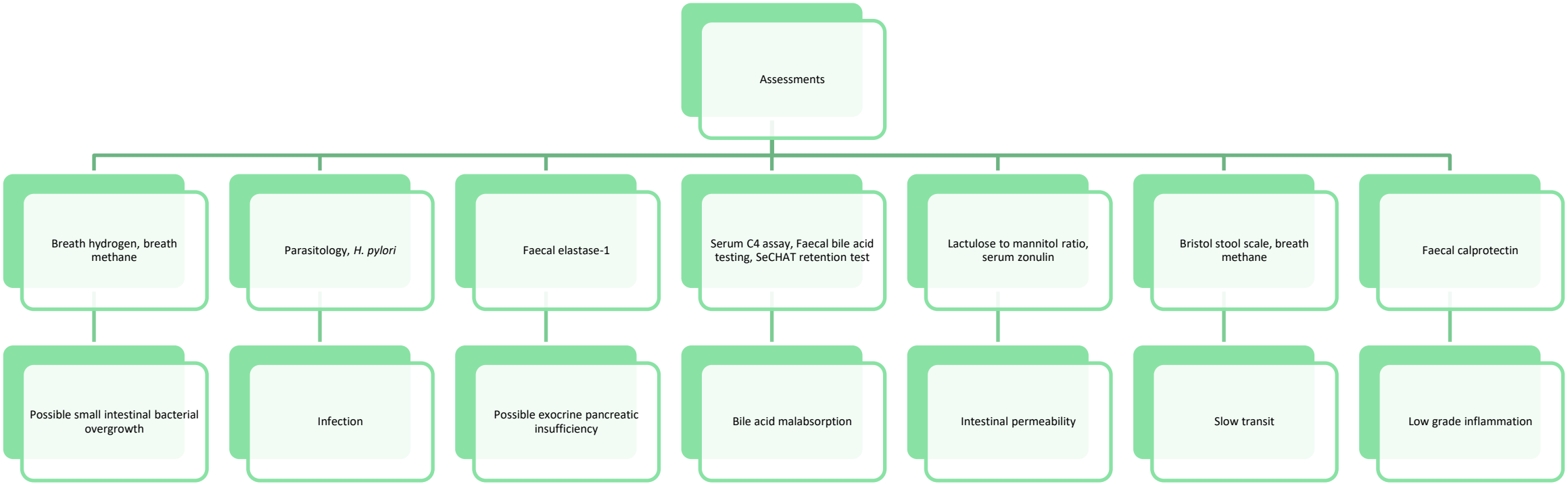
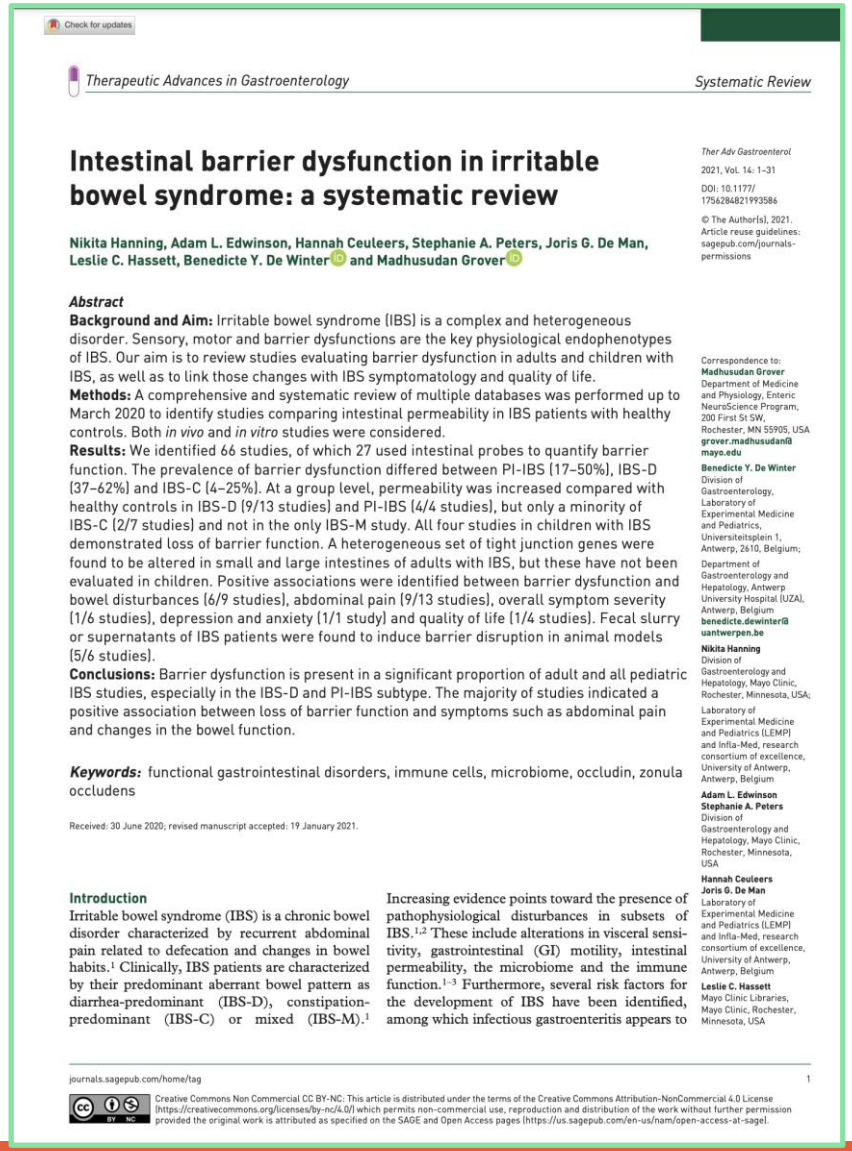
Assessment-led interventions for IBS-like symptoms



Biomarker example 1: intestinal permeability

"Barrier dysfunction is present in a significant proportion of adult and all pediatric IBS studies, **especially in the IBS-D and PI-IBS subtype.** The majority of studies indicated a positive association between loss of barrier function and symptoms such as abdominal pain and changes in the bowel function."

Therap Adv Gastroenterol. 2021 Feb 24;14:1756284821993586.



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Therapeutic Advances in Gastroenterology — *Systematic Review*

Intestinal barrier dysfunction in irritable bowel syndrome: a systematic review

Nikita Hanning, Adam L. Edwinson, Hannah Ceuleers, Stephanie A. Peters, Joris G. De Man, Leslie C. Hassett, Benedicte Y. De Winter and Madhusudan Grover

Ther Adv Gastroenterol
2021, Vol. 14: 1–31
DOI: 10.1177/175628482199358

Abstract

Background and Aim: Irritable bowel syndrome (IBS) is a complex and heterogeneous disorder. Sensory, motor and barrier dysfunctions are the key physiological endophenotypes of IBS. Our aim is to review studies evaluating barrier dysfunction in adults and children with IBS, as well as to link those changes with IBS symptomatology and quality of life.

Methods: A comprehensive and systematic review of multiple databases was performed up to March 2020 to identify studies comparing intestinal permeability in IBS patients with healthy controls. Both *in vivo* and *in vitro* studies were considered.

Results: We identified 66 studies, of which 27 used intestinal probes to quantify barrier function. The prevalence of barrier dysfunction differed between PI-IBS (17–50%), IBS-D (37–62%) and IBS-C (4–25%). At a group level, permeability was increased compared with healthy controls in IBS-D (9/13 studies) and PI-IBS (4/4 studies), but only a minority of IBS-C (2/7 studies) and not in the only IBS-M study. All four studies in children with IBS demonstrated loss of barrier function. A heterogeneous set of tight junction genes were found to be altered in small and large intestines of adults with IBS, but these have not been evaluated in children. Positive associations were identified between barrier dysfunction and bowel disturbances (6/9 studies), abdominal pain (9/13 studies), overall symptom severity (1/6 studies), depression and anxiety (1/1 study) and quality of life (1/4 studies). Fecal slurry or supernatants of IBS patients were found to induce barrier disruption in animal models (5/6 studies).

Conclusions: Barrier dysfunction is present in a significant proportion of adult and all pediatric IBS studies, especially in the IBS-D and PI-IBS subtype. The majority of studies indicated a positive association between loss of barrier function and symptoms such as abdominal pain and changes in the bowel function.

Keywords: functional gastrointestinal disorders, immune cells, microbiome, occludin, zonula occludens

Received: 30 June 2020; revised manuscript accepted: 19 January 2021.

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Introduction

Irritable bowel syndrome (IBS) is a chronic bowel disorder characterized by recurrent abdominal pain related to defecation and changes in bowel habits.[1] Clinically, IBS patients are characterized by their predominant aberrant bowel pattern as diarrhea-predominant (IBS-D), constipation-predominant (IBS-C) or mixed (IBS-M).[1]

Increasing evidence points toward the presence of pathophysiological disturbances in subsets of IBS.[1,2] These include alterations in visceral sensitivity, gastrointestinal (GI) motility, intestinal permeability, the microbiome and the immune function.[1–3] Furthermore, several risk factors for the development of IBS have been identified, among which infectious gastroenteritis appears to

Biomarker example 1: intestinal permeability

Target	Investigations	Management
Increased intestinal permeability.	• Lactulose: mannitol ratio. • Zonulin.	• Elimination diets e.g., low FODMAP, gluten-free diet, and IgG-guided elimination diet. • Glutamine. • Probiotics. • Leaky gut-targeted dietary changes.

Biomarker example 2: exocrine pancreatic insufficiency

"**Exocrine pancreatic insufficiency (EPI) is present in 5% of patients who fulfil Rome IV criteria for D-IBS**, and dyspepsia was an independent symptom strongly associated with EPI. Pancreatic steatosis was the main endoscopic ultrasound finding. **After pancreatic enzyme replacement therapy, patients had significantly improved stool frequency, stool consistency, abdominal pain, distension and IBS severity score.**"

Dig Dis Sci. 2022 Dec;67(12):5666-5675.

Digestive Diseases and Sciences (2022) 67:5666–5675
https://doi.org/10.1007/s10620-022-07568-8

ORIGINAL ARTICLE

Exocrine Pancreatic Insufficiency is Undiagnosed in Some Patients with Diarrhea-Predominant Irritable Bowel Syndrome Using the Rome IV Criteria

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Received: 28 October 2021 / Accepted: 21 February 2022 / Published online: 15 June 2022

Abstract

Background and Aims Irritable bowel syndrome (IBS) is one of the most frequent disorders in clinical practice, with a mean 7.6–10.8% worldwide prevalence. A study showed that 6.1% of patients with diarrhea-predominant IBS (IBS-D) had severe exocrine pancreatic insufficiency (EPI). We aimed to identify the prevalence of EPI based on fecal elastase stool testing (Fel-1) in IBS-D and the clinical characteristics that may predict the diagnosis of EPI.

Methods Patients aged > 18 years presenting to tertiary hospital outpatient clinics with IBS-D completed validated questionnaires and gave a stool sample where Fel-1 concentration was measured. Patients with Fel-1 < 100 µg/g represented EPI and > 100 to < 200 µg/g underwent testing for pancreatic pathology with laboratory and endoscopic ultrasound (EUS) evaluation.

Results One hundred forty patients (mean age 60 years, females 75.7%) were studied. EPI was found in 5% (95% CI 2.2–10.4), and pancreatic steatosis was the main EUS finding (71%). Dyspepsia was an independent factor associated with EPI (OR 34.7; 95% CI 4.95–366.37, $p = 0.0007$). After pancreatic enzyme replacement therapy (PERT), patients showed a significant improvement in the Bristol stool scale ($p < 0.0001$), bowel movements per day ($p < 0.005$), distension score (0.0009), pain score (0.0277) and IBS severity (0.0034).

Conclusion EPI is present in 5% of patients who fulfill Rome IV criteria for D-IBS, and dyspepsia was an independent symptom strongly associated with EPI. Pancreatic steatosis was the main endoscopic ultrasound finding. After PERT therapy, patients had significantly improved stool frequency, stool consistency, abdominal pain, distension and IBS severity score.

Keywords Irritable bowel syndrome · Exocrine pancreatic insufficiency · Pancreatic steatosis · Diarrhea · Rome IV

Introduction

Irritable bowel syndrome (IBS) is one of the most frequent disorders in clinical practice, with a mean 7.6–10.8% worldwide prevalence using Rome III criteria. It accounts for many consultations and greatly impacts patients' quality of life [1].

In clinical practice, IBS is characterized by symptoms of recurrent abdominal pain and defecation disorder, mainly affecting women [2, 3].

IBS is not only considered a diagnosis achieved after the exclusion of organic disease, but also requires a positive diagnosis using a symptom-based criterion with the most recently Rome IV classification [4].

Nevertheless, there are some clinical conditions that can simulate IBS symptoms such as colon cancer, inflammatory bowel disease, celiac disease or microscopic colitis; therefore, is important to perform a careful and deep evaluation in selected patients to rule out these confounding conditions [5]. Knowing which patients will benefit from further investigations is challenging because the diagnostic yield in IBS patients may be low. The ACG guidelines

An editorial commenting on this article is available at https://doi.org/10.1007/s10620-022-07574-w.

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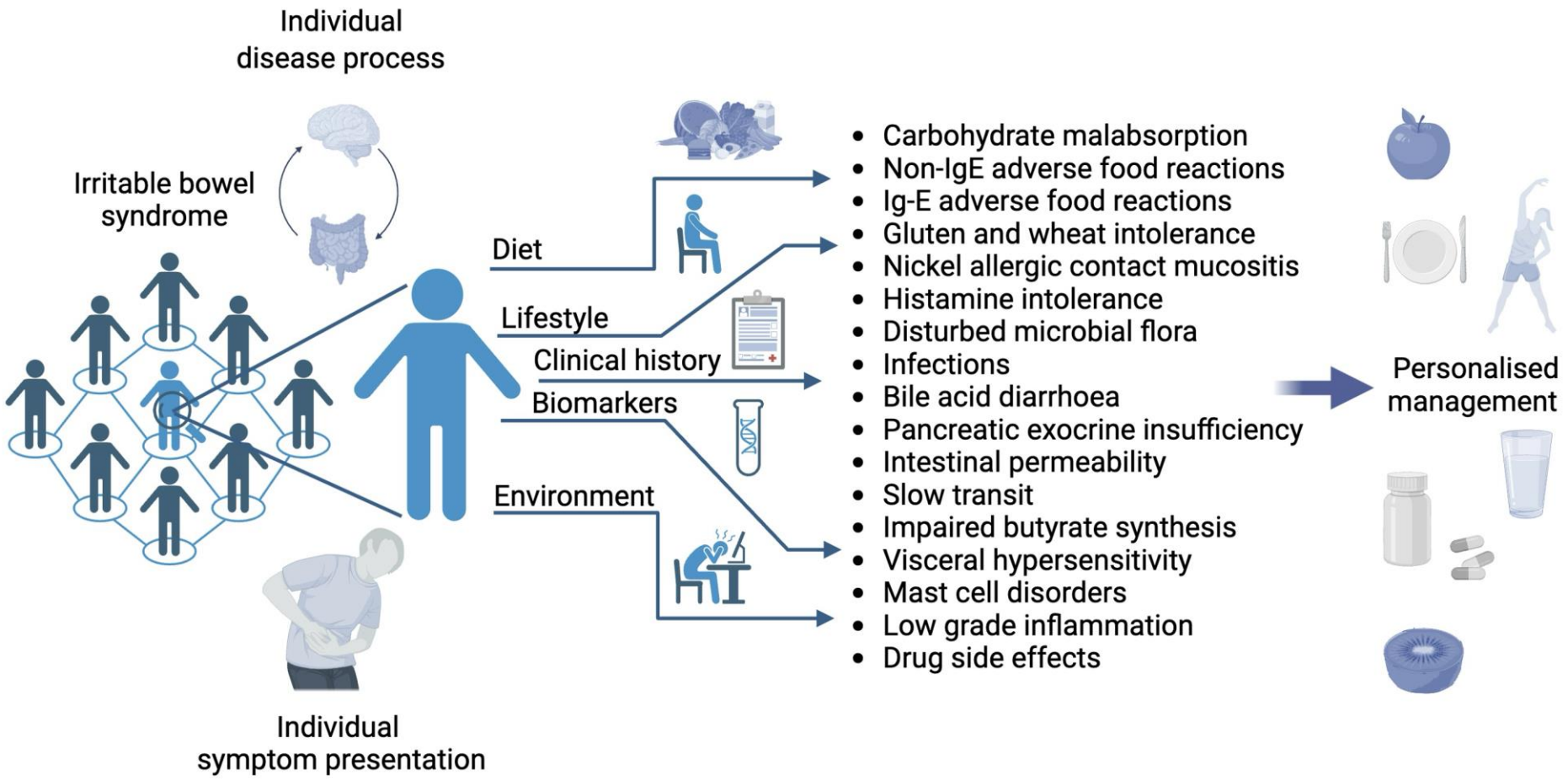
Biomarker example 2: exocrine pancreatic insufficiency

Target	Investigations	Management
Exocrine pancreatic insufficiency.	• Faecal Elastase-1. • Clinical presentation.	• Enzyme therapy. • Balanced diet, smaller more frequent meals.

Contributory factors that may explain an individual's IBS-like symptoms



"The science behind chronic illness calls for a focus not on the average but on the individual. Precisely because everyone of us is, in fact, unique, an operating model that treats us as average can't possibly be effective."

- Dr Jeff Bland, PhD