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REVIEW

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

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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 coexisting 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.

2 | DIETARY THERAPIES FOR THE TREATMENT OF IRRITABLE BOWEL SYNDROME

Due to the heterogeneity of functional gastrointestinal symptoms, it is unlikely that a single dietary therapy will be suitable for all patients.[19] As such, various dietary strategies have emerged for the treatment of gastrointestinal conditions, which are being used without uniformity across centers and regions. Table 1 outlines a range of dietary therapies available, and for each diet describes the known and/or proposed mechanisms of action, evidence of efficacy, and what clinical phenotype the diet is used for. These diets differ significantly in their dietary targets and proposed mechanisms of action. Many diets are exclusion diets followed by re-challenge to assess tolerance, while others require longer term reduction of the targeted food component. Although many of these diets are being used in patients worldwide, the supporting evidence for many is either limited or lacking.

Key Points

- Multiple dietary therapies exist for managing functional gastrointestinal symptoms.
- Despite widespread use, many diets lack scientific evidence and are used without appropriate physician guidance. The most carefully studied is the low FODMAP diet, which has evidence for efficacy and putative mechanisms.
- Dietary therapy has much promise in improving functional gastrointestinal symptoms; gastroenterologists and dietitians should work together to design studies aimed at further understanding mechanisms of action and refining therapies to enable individualized dietary advice.

2.1 | Prevalence of dietary therapies in functional bowel disorders

With the vast majority of IBS patients reporting that food exacerbates their symptoms, it is not surprising that many patients are following various forms of dietary manipulation based on information provided by the internet, lay press, advertising, or through recommendations from members of the health care system. Unfortunately, little is known of the percentage of the population using various forms of dietary therapy. The best available evidence is for the use of the gluten-free diet, where despite the controversy regarding the role of gluten in gastrointestinal symptom genesis, increasing numbers of individuals are restricting gluten. In 7798 persons in the United States in 2009-2010, prevalence of celiac disease was 0.71%. Twenty-nine of the 35 persons found to have celiac disease were unaware of their diagnosis, and of the 55 who reported following a gluten-free diet, only 6 had a diagnosis of celiac disease.[20] These data highlight that many are following the gluten-free diet without a diagnosis of celiac disease, while cases of celiac disease remain undiagnosed.

2.2 | Difficulties in assessing dietary therapies for functional bowel disorders

Dietary trials are extraordinarily difficult to undertake in a well-controlled manner, resulting in debate as to the ability to compare methodologies used for dietary vs drug therapies. This is a biproduct of a multitude of factors including difficulties in isolating single nutrient interactions among the milieu of dietary intake, difficulty in appropriately blinding participants, and high placebo and nocebo response rates.[21] Dietary studies have been undertaken in four main ways; firstly, through observational studies or clinical audits[22]; secondly, through using food challenge[23]; thirdly, through comparisons to another diet such as the current standard dietary therapy[24] or habitual diet[25] or sham diet[26] or another therapeutic diet[27]; and finally, through comparing extreme's eg, low vs high FODMAP (fermentable oligo- di- mono-saccharide and polyols) diets.[28] All modes of assessment have strengths and limitations, and provide different insight. For example, while comparing extremes is advantageous to maximize the likelihood of achieving a change, it may reach differences that are not usually seen in real-life practice; alternatively, the use of another therapeutic diet as a comparison potentially reduces the placebo response, but if both diets are effective then the change may be muted. It is likely that studying the same diet in a variety of ways will produce the most clarity in answering research questions, such as clinical audits providing initial suggestion of efficacy which is then followed by randomized controlled trials comparing a new dietary therapy to previous standard therapy.

Research publication trends noted by Dimidi et al (2017) show that while fiber was frequently studied in the last millennium, and probiotics frequently studied in the 2000s, these have now diminished and publication focus has turned to the low FODMAP diet.[29] The low FODMAP diet is one of the most extensively studied diets for FBD, with multiple randomized controlled trials conducted worldwide.[24,26,30,31] These studies suggest improvement in 50%-81% of patients with IBS[32] but this magnitude of benefit has been questioned for a number of reasons. The studies have been criticized due to small subject numbers, potential for unblinding, and the possibility for placebo response to influence the reported response rates.[33,34] Although not directly comparable to a placebo-drug, a "sham" diet used by Staudacher et al (2017) provided adequate relief in 38% of patients compared 57% with the low FODMAP diet (intention-to-treat analysis $P = .051$), providing a 19% benefit over the "sham" diet.[26] Placebo response in IBS is high, ranging from 3% to 84%,[35] with additional challenges for the design of dietary intervention trials which should be considered in the interpretation of study results[33] and are discussed below.

Multiple studies have also assessed the use of the gluten-free diet,[23,36–39] but criticism has drawn attention to the difficulty of isolating gluten from other components in wheat, as well as difficulty in appropriately excluding celiac disease prior to subject enrolment.[40] Similarly, many studies have investigated the role of increased or decreased intake of various forms of dietary fiber, but inconsistencies in the type of fiber used, or population studied makes formation of

guidelines difficult.[41] To date, the best evidence is for the use of psyllium fiber in IBS which has been reviewed elsewhere.[29,42] Prebiotic fiber supplements provide promise due to their theoretical beneficial effect on the colonic microbiota, but overlap of some prebiotics with FODMAP composition (fructans and galacto-oligoasaccharides) suggests some varieties may worsen symptoms of IBS.[29] There is also potential for the use of strain-specific probiotics to target-specific symptom types, but current evidence is limited by lack of intention-to-treat analyses and inconsistencies in the types of single- or multi-strain probiotic used.[29] Other dietary therapies receiving attention include the specific carbohydrate diet, diets for the treatment of small intestinal bacterial overgrowth (SIBO), the paleo diet, low histamine or food chemical diets and modified protein diets, none of which have a significant body of literature or proven mechanisms of action.

2.3 | Order of use and targeting symptom phenotypes in functional bowel disorders

The range of dietary therapies available creates the issue of choosing which therapy to trial in the individual and if unsuccessful, whether another dietary therapy may be worthwhile. The National Institute for Clinical Excellence (NICE) guidelines are considered as first-line

TABLE 1 Dietary therapies for the management of gastrointestinal symptoms

Diet	Dietary details	Proposed mechanisms of action	Condition	Evidence for efficacy
Diets with a primary focus on eating pattern				
The NICE guidelines	The NICE guidelines were published in 2008.[115] Recommendations: regular meal pattern; adequate fluids; limit caffeine*, alcohol*, fat*, fizzy drinks; reduce fiber and resistant starch; increase soluble fiber where needed; limit fruit to 3 portions per day.[115,116] *Singular reduction of fat, alcohol or caffeine also are also used in practice as dietary therapies but will not be covered as stand-alone therapies in this review.	Based on available evidence and group opinion. Clear mechanisms of action have not been substantiated.	IBS	**Comparative trials:** Three studies have compared the NICE guidelines with the low FODMAP diet.[24,31,99] The low FODMAP diet was shown to be more effective than the NICE guidelines in one study,[99] and found to have similar efficacy in another study.[24] A third study reported similar efficacy in overall symptoms, but greater improvement in individual IBS symptoms, particularly abdominal pain and bloating, with the low FODMAP diet compared to the NICE guidelines.[31]
Diets with a primary focus on carbohydrates and/or fiber				
Modified fiber diets	Modification of various components of fiber can be made through addition of a fiber supplement, or individualized adaptation of the patients' dietary fiber intake (through increased or decreased fiber intake). Current guidelines for IBS suggest increasing dietary fiber intake where applicable and considering use of supplementation with up to 24 g/day of linseeds.[43]	Highly fermentable soluble (eg, fructo-oligosaccharides, galacto-oligosaccharides, resistant starch, pectin, inulin, guar gum) and fermentable insoluble (eg, wheat bran, lignin) fibers are likely to create additional gas production within the large intestine and, therefore, may not be well tolerated in patients with IBS.[117] On the contrary, insoluble, non-fermentable fibers (eg, cellulose, sterculia, methylcellulose) create low amounts of gas and are likely to be better tolerated in IBS,[117] although this has not been extensively studied. Intermediately fermentable soluble fibers such as psyllium may have side-effects of gas production, although studies in IBS generally report positive effect.[117]	IBS	Dietary fiber supplements have shown variable efficacy, likely due to the predominant symptom type studied as well as the nature of the fiber itself. **Meta-analysis:** A meta-analysis of 14 RCTs of supplemental fiber in patients with IBS has been conducted.[118] Fiber was found to have a statistically significant positive effect overall compared to placebo, with a number needed to treat of 10 (95% CI 6-33). Comparing bran to soluble fiber (psyllium), bran had no significant effect, while soluble fiber was effective with a number needed to treat of 7 (85% CI 4-25).[118] Similar results were seen in an earlier meta-analysis finding psyllium, and not bran, was effective in IBS.[41] Ground linseeds may be beneficial in constipation predominant IBS.[43]

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TABLE 1 (Continued)

Diet	Dietary details	Proposed mechanisms of action	Condition	Evidence for efficacy
The low FODMAP diet	Short-term (2-6 week) restriction of foods high in fermentable carbohydrates, followed by re-challenges to assess tolerance. Food groups requiring most modification include fruits, vegetables, and grains. Wheat intake is reduced, but not strictly gluten-free. Food analysis of FODMAP content has been published in peer review literature[85–89] and in lay-terms for patients.[119] Clearly defined re-challenge protocol has been published based on clinical expertise.[105]	Poor absorption of FODMAPs in the small intestine results in an osmotic effect causing increased water delivery into the lumen as shown in ileostomates[96] and via use of MRI.[120] Delivery of FODMAPs to the large intestine increases colonic fermentation resulting in gas production as shown by breath testing[97] and MRI.[120] Colonic hypersensitivity to distention has been suggested whereby symptoms increased in IBS patients when distention has been shown on MRI.[121] A phenomenon also seen in rats.[122] Emerging evidence that FODMAPs modulate immune activation.[28] Recent data show postprandial gastric pressures to be higher following fructan vs control (glucose), and an increase in symptoms was noted within 30 min.[123] These results suggest that FODMAPs may also influence the upper gastrointestinal tract through neural or hormonal differences.	IBS	**Meta-analysis:** A systematic review published in 2015 was unable to complete a meta-analysis and concluded that more evidence was needed prior to routine use of the diet in patients with IBS.[34] However, efficacy in IBS patients was supported by recent meta-analysis published in 2016 and 2017,[45,124,125] highlighting the fast-pace of research in the field. Long-term adherence to the diet has been featured as an area that requires further investigation. **Randomized controlled trials:** Studies in adults suggesting positive effect of the low FODMAP diet on IBS symptoms compared to habitual diet[25,30,95,126] and compared to a sham diet[26]; three studies have compared to the NICE guidelines with mixed results (as above)[24,31,99]; two compared to a high FODMAP diet showing a positive effect on symptoms[28,97]; one to the specific carbohydrate diet showing positive effect on symptoms[27]; one showing similar efficacy compared to gut-directed hypnotherapy[100]; and one showing worsened symptoms with fructan compared to placebo supplementation.[60] One study in pediatrics has also shown positive effects on symptoms.[58] **Long-term studies:** Two recently published papers showing efficacy of the low FODMAP diet in the long-term following re-challenge.[50,51]
			Quiescent IBD with FBD	**Meta-analysis:** Meta-analysis supports the use of the low FODMAP diet in quiescent IBD, but acknowledges further studies are required.[127] **Randomized controlled trials:** One RCT showing benefit to functional symptoms.[66] **Retrospective studies:** Three studies suggesting benefit to functional symptoms.[22,74,75] **Proof-of-concept:** Re-challenge study in patients with IBD showed symptom induction with 3-day fructan challenge.[72]
SIBO diet	Guidelines are variable. As per Rezaie et al (2016), elemental diet can be used to eradicate SIBO,[128] followed by the low FODMAP diet for maintenance therapy.[129] Poorly defined length of dietary modification. Largely non-evidence based: http://www.siboinfo.com/diet.html	Bacterial overgrowth in the small intestine results in increased fermentation of simple sugars and more complex carbohydrates. Theoretically, a diet low in fermentable foods may decrease the chance of bacterial overgrowth by creating a less-favorable luminal environment for bacteria.[129]	IBS	Controversy exists for the role of SIBO in the pathophysiology of IBS,[130] in part due to the difficulties in obtaining accurate diagnosis of SIBO.[131] Despite such controversy, SIBO diets exist within the community, most of which lack scientific substantiation. Most commonly, the low FODMAP diet, specific carbohydrate diet, among others, have been suggested, although none have been studied specifically in a population of patients with supposed SIBO.

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TABLE 1 (Continued)

Diet	Dietary details	Proposed mechanisms of action	Condition	Evidence for efficacy
Specific carbohydrate diet (SCD)	The SCD excludes refined sugar and complex carbohydrates.[132] All grains, potatoes, milk, and processed meats are excluded.[133] Poorly defined length of dietary modification. Multiple versions of the SCD exist, including modified SCD diets such as the "GAPS diet" (Gut and Psychology Syndrome diet). Largely non-evidence based: http://www.breakingthevicioussycle.info/ http://www.gapsdiet.com/	Proposed that malabsorption of complex carbohydrates and sugars could lead to bacterial dysbiosis contributing to intestinal inflammation.[132]	IBS	Despite advocates for the use of the diet in IBS,[132] minimal evidence exists for its use for functional symptoms in the absence of inflammation.[134] **Comparative study:** A single-blinded study provides preliminary results comparing the low FODMAP diet and SCD in 60 IBS patients. The low FODMAP diet improved symptoms from baseline, while the SCD only showed a trend toward a reduction. However, of concern, after 3 months the SCD resulted in significant reductions in folate and Vitamin D which was not seen with the low FODMAP diet.[27] While this study provides preliminary data, more insight is needed into the effect of the SCD on symptoms and any potential side-effects including nutritional adequacy.
Paleolithic (Paleo) diet	Restricts intake of all grains, legumes, potatoes, and dairy products. Encourages a high fiber diet with consumption of lean non-domesticated meats and non-cereal plant-based food.[133] Poorly defined length of dietary modification. Largely non-evidence based: http://thepaleodiet.com/	The underlying hypothesis is that the human gastrointestinal tract is poorly adapted to the modern diet based on agriculture. Exposure of modern foods that were not available during evolution is thought to lead to disease, although exact mechanisms are not defined.[133]	IBS IBD	Anecdotal evidence for use in IBS only. Use of the diet has been encouraged largely through lay and celebrity advocates.[135] There are no published studies for the use of the paleo diet in the management or prevention of IBD.[133]
Diet for sucrase-isomaltase deficiency	Initial restriction of sugars and starch followed by re-introduction to test tolerance.	Reduced small intestinal activity of glucosidase, results in disaccharide (particularly sucrose) and starch malabsorption, resulting in osmotic diarrhea and abdominal pain, features of IBS.[136]	IBS	The role of sucrase-isomaltase deficiency and the potential for dietary management in irritable bowel syndrome is poorly established. **Trials assessing effect by genotype:** Genetic variants more common in IBS patients compared to healthy controls.[136]
Diets with a primary focus on proteins				
The gluten-free diet	Involves strict avoidance of all gluten-containing grains, including wheat, barley, rye, and oats. The diet also requires the avoidance of small traces of gluten found in packaged foods. Unknown level of dietary restriction and length of modification required in patients with IBS. No published guidelines on when or if to trial re-introduction of gluten to test tolerance (NB: strict life-long adherence to gluten-free diet recommended for patients with diagnosed celiac disease).	Mechanisms have not been clearly identified. Proposed mechanisms include alterations to the intestinal barrier caused by gluten, with potential for genetic susceptibility to be a factor.[137] Another mechanism may be innate immunity induced by amylase trypsin inhibitors which co-exist with gluten.[138] Biomarkers including increased CD14, lipopolysaccharide-binding protein, and antibody reactivity to microbial antigens, have been shown in patients symptomatic to wheat suggestive of systemic immune activation.[139] Dose-response is unknown.	IBS	Uncertainty exists of the exact component in a gluten-containing diet responsible for symptom induction. There is difficulty in separating gluten-mediated effects from other components present in wheat, eg, fructan (FODMAP) and amylase trypsin inhibitors, as well as difficulty in ensuring adequate exclusion of celiac disease.[40,140] This has resulted in various names for the condition such as non-celiac gluten sensitivity, or non-celiac wheat sensitivity. Elucidation of the mechanism of action will provide the correct name.[140] The most important clinical issue is the appropriate exclusion of celiac disease before the start of a gluten-free diet. **Randomized controlled trials:** Four RCTs have shown no evidence of symptom genesis with gluten.[23,36–38] On the contrary, two RCTs have shown worsened symptoms with a gluten-containing diet.[39,137] The conflicting results highlight the challenges in design of clinical trials to clearly define the role of gluten or other components in wheat.

(Continues)

TABLE 1 (Continued)

Diet	Dietary details	Proposed mechanisms of action	Condition	Evidence for efficacy
				Non-randomized clinical trials: Two studies have shown improved symptoms following 4-6 month use of the gluten-free diet in IBS.[141,142] **Trials assessing effect by genotype:** One RCT showed greatest effect in HLA-DQ2/8-positive patients[137]; another showed improvement in 60% of HLA-DQ2-positive patients and only 12% who were HLA-DQ2-negative.[141] While another study showed no association between genotyping and response.[142] **Animal models:** Alterations in gut function have been observed in mice in response to gluten challenge, including muscle hyper contractility in HLA-DQ8 transgenic mice,[143] and increased transcellular macromolecular transport in HLA-DQ8/HCD4 mice.[144] How this translates in patients with IBS requires elucidation.
Reduced resistant protein diet	Reduced protein intake while increasing intake of oligosaccharides, resistant starch and non-starch polysaccharides. Protein reduction may involve specific focus on reducing aromatic and sulfur-containing amino acids.	Based on the principle that a diet containing reduced amounts of carbohydrate, with high protein quantity will alter the colonic microbiome, in turn favoring a pathogenic and pro-inflammatory profile. Metabolites (eg, hydrogen sulfide and ammonia phenols) are then increased which cause mucosal inflammation and modulate the enteric nervous system and motility.[54]	IBS	No clinical data from human trials. **In vitro:** Hydrogen sulfide production by human fecal microbiota was reduced by resistant starch and fructo-oligoasaccharide, suggesting a role of diet in modulating hydrogen sulfide production.[145] **Animal models:** Hydrogen sulfide shown to effect visceral hypersensitivity in mice, which may have implications for patients with IBS.[146]
Diets with a primary focus on bioactive food chemicals				
Low capsaicin diet	Reduction of capsaicin containing foods, a bioactive compound present in capsicum/peppers and chilli.	Capsaicin may stimulate TRPV1 channels[147] causing a sensation of scalding and/or pain.	IBS	Small number of trials showing capsaicin consumption increases visceral hypersensitivity and pain sensation in IBS.[101,148] Chronic chili consumption offers a potential method to improve tolerance.[111] **Randomized controlled trial:** Hypersensitivity was seen in patients with IBS-D consuming chilli.[101] **Comparative study:** Capsaicin induced visceral hypersensitivity in IBS patients compared to healthy controls.[147] **Self-reported questionnaire:** In a study of 197 IBS patients, 42% reported capsaicin-containing foods to cause IBS symptoms.[2]
The low Amine/ Histamine diet	Avoidance of aged cheeses, fish, processed meat, some vegetables, fermented soy products, other fermented foods (eg, sauerkraut), alcoholic beverages, and vinegars.[92,149] Difficult to obtain accurate food composition data as amines increase as the food matures. Initial restriction followed by re-challenges to assess tolerance.	Impaired histamine degradation may occur in patients with reduced activity of diamine oxidase. The resulting excess of histamine may lead to symptoms mimicking allergic type reactions, including diarrhea, gastrointestinal upset as well as extra-intestinal symptoms.[92]	IBS + extra-intestinal symptoms	There is scarce high-quality evidence available for the use of a low histamine diet. However, the diet is used in the community. **Self-reported questionnaire:** In a study of 197 IBS patients, 115 patients (58%) reported foods rich in amines to cause IBS symptoms.[2]

(Continues)

TABLE 1 (Continued)

Diet	Dietary details	Proposed mechanisms of action	Condition	Evidence for efficacy
The low food chemical diet or "elimination diet"	The complete elimination diet was developed by researchers at the Royal Prince Alfred Hospital in Australia. It restricts dietary salicylates, amines, monosodium glutamate, benzoates, propionates, sulfites, nitrates, sorbic acid, antioxidants, and colors. However, comprehensive food composition data are not available. Recent data of the salicylate content of 100 foods have been published[93] The elimination phase usually for 2-4 weeks followed by re-challenges.	The food chemicals restricted on the diet are thought to induce non-specific antigen-induced pseudo-allergic hypersensitivity.[150,151]	IBS + extra-intestinal symptoms eg, urticaria, headache, eczema, rhinitis, nasal congestion, postnasal drip among others[47]	No controlled trials have been published in IBS,[152] hence mechanisms and efficacy are poorly understood. Additional concerns have been raised regarding its nutritional adequacy when applied in children.[153] However, it has been used in clinical practice, particularly in Australia since its development in the 1980's.[47]

FODMAP denotes fermentable oligo- di- mono-saccharides and polyols; GAPS denotes gut and psychology syndrome diet; IBD denotes inflammatory bowel disease; IBS denotes irritable bowel syndrome; IBS-D denotes diarrhea predominant irritable bowel syndrome; MRI denotes magnetic resonance imaging; NICE diet denotes National Institute for Clinical Excellence diet; RCT denotes randomized controlled trial; SCD denotes specific carbohydrate diet; SIBO denotes small intestinal bacterial overgrowth.

therapy by the British Dietetic Association,[43] although some have argued that the low FODMAP diet should now be considered as a first line.[44,45] Variations in recommendations exist between countries, partially related to access to suitably trained dietitians.[46] Specific symptom phenotypes may indicate to the prescriber which diet is most likely to be successful. For example, the use of low histamine or low chemical diets which are generally targeted toward patients who exhibit gastrointestinal symptoms combined with extra-intestinal symptoms such as eczema, rhinitis, nasal congestion, and headaches.[47] Prediction of response and individualized dietary therapy is discussed below.

3 | SAFETY ISSUES RELATED TO DIETARY THERAPIES IN IRRITABLE BOWEL SYNDROME

As with side-effects from drugs, dietary therapies have specific safety issues. Nutritional adequacy is one key concern, as well as the potential to negatively impact the gastrointestinal microbiota, mental health, and quality of life. Hence, dietary therapies should only be used with the appropriate clinical diagnosis, if sound evidence exists, and if they can be undertaken in a safe manner. Implementation of any dietary therapy should only be considered following medical examination with exclusion of other conditions, eg, exclusion of celiac disease.

3.1 | Nutritional adequacy

Although patients with IBS state that they avoid suspected trigger foods due to intolerance, current data suggest this does not appear to have a significant impact on their overall nutrient intake.[48] Any diet that modifies sources of key nutrients, such as dairy products for calcium, should ensure suitable alternatives are available. Exclusion diets which restrict whole food groups such as the specific carbohydrate or paleo diets are likely to have pronounced effects on nutrient intake, although this has not been specifically studied. Preliminary data of 60 IBS patients randomized to 3 months of either the low FODMAP diet or the specific carbohydrate diet, showed that the specific carbohydrate diet resulted in significant reductions in folate and vitamin D levels, reductions that were not seen in the low FODMAP diet group.[27] This highlights the restrictive nature of the specific carbohydrate diet and its potential to cause adverse events. Likewise, patients with celiac disease following a gluten-free diet had more inadequacies (including folate, calcium, iron, and zinc) than the general population and dietary intake was similar between newly diagnosed and long-term patients.[49] Whether the same nutrient deficiencies occur in patients with IBS utilizing the gluten-free diet, is unknown and is likely dependent on the level of gluten restriction used. Changes to nutrient intake have also been noted following institution of the low FODMAP diet, with reductions in total energy, carbohydrate, fiber and calcium intake reported during the initial restrictive phase.[24,25,31] These effects may resolve following re-challenge, as suggested by data to date from long-term studies.[50,51] It may be that the institution of any diet and/or involvement in a dietary study has effects on total energy intake, as total energy intake was also reduced in comparison groups randomized to the NICE guidelines.[24,31] The potential to reduce total energy, macro- or micro-nutrient intake with institution of any diet, as shown in the above-mentioned studies, highlights the need for close dietetic monitoring and long-term follow-up with patients undertaking dietary modification.

The length of time the patient is required to follow any dietary intervention also plays a role in the level of concern regarding the nutritional adequacy of the diet in question. For example, following re-introduction of FODMAPs, 82%-84% of patients report that they continued on an adapted low FODMAP diet, with wheat, dairy products, onion, and garlic most commonly not re-introduced.[22,50] Data to date suggest that long-term dietitian-taught use of the low FODMAP diet does not affect overall nutritional adequacy,[50] although it is not known how this relates to those who are self-taught.[49]

3.2 | Alterations to the microbiome

Diet has a major influence in defining gut microbial phylogeny and activity,[52] through direct effects on composition and energy supply, as well as indirect effects through alterations to pH and transit time.[53] Carbohydrates are well documented to exert effects on total bacterial abundance via acting as substrates for fermentation and, for some, on relative abundance of bacteria via so-called "prebiotic" effects. Hence, it is likely that many of the dietary therapies that alter carbohydrate intake (see Table 1)—the low FODMAP diet, specific carbohydrate diet, SIBO diets—will all have an impact on the microbiota profile. However, the location of their effect on the microbiota along the gastrointestinal tract may be divergent, although this has not been studied.[53] A diet with reduced composition of resistant proteins may also alter the microbial profile.[54] The clinical significance of these changes, especially in the long term following re-introduction of food components is unknown.

Alterations to the microbiome have been noted with the gluten-free diet. For example, 21 healthy controls followed a gluten-free diet for 4-weeks, resulting in changes to the microbiota including reducing the *Clostridia* class.[55] Another study of 10 healthy controls noted reductions in *Bifidobacterium*, *Clostridium lituseburense*, *and Faecalibacterium prausnitzii* proportions.[56] It is likely that there is a multitude of dietary factors that may influence the microbiota following dietary restriction, even if only one dietary component is targeted. Using the gluten-free diet as an example, is the alteration in the microbiota composition a consequence of removing the gluten itself; removing the gluten-containing food (eg, wheat); introduction of foods that gluten is replaced with (often high in sugar and fat and low in fiber); or a consequence of all of these dietary changes combined?

There has been particular concern regarding the low FODMAP diet effects on the microbiota, in part because it is the most studied dietary intervention to date,[25,26,28,57-61] and is currently widely used. A number of changes have been described with many showing reductions in *Bifidobacteria*, although data have been inconsistent. Differences in results between studies may be related to regional dissimilarities in baseline microbiota and differences in what comprises a "typical" diet in the respective countries. For example, the typical diet in the United Kingdom had higher quantities of galacto-oligosaccharides (mean of 2 g per day)[25] likely due to the more frequent use of legumes, compared to the typical Australian diet (mean of 1 g/day).[57] It is possible that differences in baseline microbiota result in divergent responses of the microbiota to dietary change. Alterations to the microbiota profile then have potential effects on fermentation by-products including short-chain fatty acids (SCFA). Following the low FODMAP diet, reductions have been seen in total fecal SCFAs and specific types including Butyrate, a SCFA thought to have protective health effects.[60,61] However, data on whether significant changes in SCFA's occur are conflicting[25,32,57] possibility related to small subject numbers and differences in methodology used.

While many suggest that the low FODMAP diet could alter the colonic bacteria in a direction that may be harmful to health (through reduction in *Bifidobacterium*); others have suggested potential beneficial effects. Following a low FODMAP diet, McIntosh et al (2016), described potential for both negative and positive alterations in the bacterial profile, including a decrease in relative abundance of *Bifidobacteria* thought to have potential harmful effects, with a simultaneous positive increase in abundance of *Adlercreutzia*, a bacteria able to consume hydrogen which otherwise would be available for production of hydrogen sulfide and methane.[28] Moreover, results to date are based on fecal bacteria profiles which do not provide information about the mucosa-associated profile.[62]

Potential effects from dietary therapies may be modulated via use of supplemental probiotic or prebiotic supplementation.[63] For example, 10-day 16 g fructo-oligosaccharide supplement in conjunction with the low FODMAP diet increased bacterial abundance, although it did not improve SCFA production.[60] In another study, 4-week probiotic supplementation (VSL#3) has shown promise in increasing *Bifidobacterium* compared to placebo when used in conjunction with the low FODMAP diet.[26] These therapies provide promise that microbial alterations caused by dietary modification can be mitigated if necessary.

3.3 | Effect on quality of life

Diet has potential to alter quality of life in one of two directions. Dietary therapy resulting in an improvement of troublesome gastrointestinal symptoms may improve quality of life. On the contrary, dietary restrictions imposed on a patient may affect socialization and reduce quality of life.

Health-related quality of life was found to be similar in patients following a gluten-free diet with non-celiac gluten/wheat sensitivity compared to those with celiac disease. However, compared to healthy controls, patients on a gluten-free diet did report lower physical health, health perception, increased pain, and reduced social function.[64] Whether these differences were related to poorly controlled symptoms on the gluten-free diet, or due to the restrictions of the diet itself are unknown. The low FODMAP diet has shown positive improvements to quality of life in patients with IBS compared to those not receiving dietary therapy,[51] compared to a modified NICE diet,[65] and in IBD patients compared to those receiving a normal diet.[66] Using the interference with life in general data from the IBS-severity scoring system, one study showed improvement on the low FODMAP diet compared to baseline.[60] In another study which showed no difference in symptom score between

the low FODMAP and NICE diets, both diets reduced interference with life in general, with no difference between the two diets.[24] Long-term follow-up suggests the diet is more expensive and patients have increased difficulty in eating out and while travelling,[50] which may negatively impact quality of life. Further correlations are required to understand the short- and long-term effect of the low FODMAP diet on quality of life.

Obsessions with one's diet or for choosing foods solely for "health" aspects, has given rise to a new form of eating disorder termed "orthorexia nervosa." As distinct from other eating disorders focused on quantity of food, orthorexia nervosa occurs where the individual is overly concerned about the quality or health aspects of the food they consume.[67] A prevalence of 7%-58% has been described in the general population,[68,69] and this may be higher in the FBD population. The restrictive nature of diets used for management of gastrointestinal symptoms, which classify foods into safe and unsafe based on their likelihood to effect symptoms, leads to concern that dietary therapies may intensify the prevalence of this disordered eating behavior.

4 | DIETARY THERAPIES FOR THE TREATMENT OF FUNCTIONAL SYMPTOMS IN PATIENTS WITH QUIESCENT IBD

Irritable bowel syndrome-like symptoms in patients with IBD in "remission" are very common, reported to be as high as 35%-45%.[17] The pathophysiology of IBS symptoms in quiescent IBD is poorly understood,[70] could vary between individual patients, and could have important implications regarding diet therapy. In general, two main mechanisms have been proposed, – overlapping or "true" IBS occurring in IBD, or IBS symptoms triggered, at least in part, by ongoing subtle inflammation.[71] Understanding these entities is complicated partially because IBD remission has been defined in several ways; clinical remission (absence of symptoms), endoscopic remission (mucosal healing), or deep remission (no symptoms and mucosal healing). Whether these different diagnostic criteria are important when choosing diet therapies to manage IBS symptoms in unknown, but as discussed below, this could have important implications regarding efficacy and safety.

With the high frequency of IBS symptoms in quiescent IBD, the low FODMAP diet is now being integrated into clinical practice for control of functional symptoms in IBD patients. A small body of evidence suggests similar benefits in quiescent IBD patients as seen with IBS.[66,72-75] However, theoretical concern exists for the potential lowering of SCFA with use of the low FODMAP diet, as reduced SCFA has been implicated in increasing susceptibility to colitis in mice.[76] Additional concern exists for the proposed direct and indirect impact on the immune response due to reduced intake of sources of prebiotics.[77] This highlights the need for high-quality studies prior to implementation of dietary manipulation into routine clinical practice.

Presumably, any diet that may be used in the presence of active inflammation may be continued throughout remission. Various diets to target active inflammation or to prevent relapse in IBD have also been suggested, including the specific carbohydrate diet (Table 1), exclusive or partial enteral nutrition, reducing intake of dietary emulsifiers,[78,79] and various versions of "anti-inflammatory diets."[80-82] The role of diet in active IBD is beyond the scope of this review and has been reviewed elsewhere,[83,84] but emerging data indicate a potential role of diet in prevention of relapse. Increasing intake of putative "anti-inflammatory" foods (fiber, prebiotics, probiotics, omega-3 fatty acids, antioxidants) while simultaneously reducing putative "pro-inflammatory" foods (red meat, sugar, alcohol) for 6 months prevented increases in colonic inflammation as measured by fecal calprotectin compared to typical Canadian healthy eating advice in patients with ulcerative colitis.[80] In healthy controls, the "FIT" (Food Influence on the intestinal microbioTa) diet increased microbial richness and decreased fecal calprotectin, although data in ulcerative colitis are pending.[81] By modulating bacterial profiles and their metabolites, these "anti-inflammatory" diets may be able to alter the inflammatory process hence provide an opportunity to use diet in prevention of relapse.

5 | SAFETY ISSUES FOR THE USE OF DIET IN IBD

Similar concerns exist for the use of dietary therapies in patients with quiescent IBD as in patients with IBS. Moreover, patients with IBD may have additional nutritional requirements related to medication use or previous surgery. Therefore, nutritional adequacy must be a primary consideration in IBD patients before utilizing any restrictive diets. Any modifications to the diet must take this into consideration and ensure nutritional adequacy is still achievable.[84]

6 | PREDICTING RESPONSE TO DIETARY THERAPIES

Table 2 describes a number of techniques that identify putative targets and/or modalities that may be useful in predicting response to various forms of dietary therapies. It highlights the existing evidence using each technique and some of the major limitations. With the many diet types available, and large inter-individual variability, it is likely that multiple ways to predict response may be required. Encouragingly, more dietary studies are being designed in ways to include assessment of potential areas to predict response, which may guide future clinical practice.

Predicting response to dietary therapies would assist in decision making for clinicians to target therapy to the individual in several important ways. Firstly, will dietary therapy be successful in a particular individual and if so, which type of diet? Can we predict who will respond to a particular dietary therapy, and importantly who will not? In those who are unlikely to respond, would another diet therapy be more effective or is another therapeutic modality better indicated? Secondly, what level of restriction would the dietary therapy need to be for the

individual to benefit? Finally, could the therapy type be modified for the individual rather than using blanket one-size-fits-all approaches? Modifying diets to the individual has potential to reduce the level of restriction required, for example, targeting only sorbitol and fructans instead of all FODMAPs; or targeting only amines and glutamates instead of all bioactive food chemicals. The ability to predict response to dietary therapy may also assist to reduce patients "diet shopping" and following multiple dietary restrictions simultaneously leading to dangerously over-restricted diets. In addition, it may encourage the patient to undertake dietary therapies with the guidance of their doctor and/or dietitian rather than using self-diagnosis, trial and error, or "Dr Google."

7 | FUTURE DIETARY RESEARCH—OPTIMIZING RESEARCH DESIGN

As discussed above, studies assessing the effect of dietary change are notoriously difficult to undertake.[21] Key steps for the evaluation of dietary modalities are outlined in Figure 1 and should consider the following:

7.1 | Subject numbers

Challenges in designing and undertaking dietary studies have led to small subject numbers in the vast majority of studies. As compared to pharmacotherapy trials, along with difficulties in creating true placebo therapies, a lesser amount of funding available to study the role of diet creates an additional challenge.

7.2 | Food composition analysis

Comprehensive food analysis of food components under question should be one of the first priorities in order to evaluate the effects of any dietary concept. The importance of accurate food composition data, using established food analysis techniques, has been made clear with the evolution of the low FODMAP diet. Key food composition papers were published near to the time that the diet was conceptualized,[85-87] and subsequent papers have been published,[88-90] showing how inaccurate previously published food lists were.[46] This has provided research groups worldwide with the FODMAP composition of foods, allowing for more consistent dietary modifications to be used across research studies. Techniques are also well established for the analysis of gluten content of foods, but unfortunately, techniques for the analysis of many other food components have not been established, and ongoing analysis of a wide range of foods for any component is laborious and costly. But, without this food composition data, achieving adequate numbers of research studies addressing the role of a particular diet in any disease is unobtainable. For example, food composition data for a low histamine diet are lacking, and available food lists are conflicting. While one source suggests that yoghurt is a source of histamine,[91] another does not.[92] Malakar et al (2017) highlighted the variation in quantities of salicylate content of foods reported in the literature, suggesting that in part variation is due to the measurement techniques used.[93] Additionally, how the food is prepared is of importance, as shown by peeled vs unpeeled apple containing 2.93 and 9.03 mg/kg salicylate respectively.[93]

7.3 | Provision of dietary therapy

Two main approaches can be taken in regard to design of dietary studies. Firstly, provision of dietary advice where the therapy under question is given through careful education of participants. Such an approach has been used successfully in studies investigating the low FODMAP diet and provides data more closely related to a "real-life" scenario as would occur in clinical practice.[22,24,25,28,94,95] Secondly, more controlled studies are undertaken involving the provision of the diet,[30,96,97] which provides major advantage in proving a concept by increasing the level of dietary control, reducing the effects of other potential confounders, and improving blinding. It can also ensure that other dietary constituents are kept the same between treatments, for example matching the fiber content. The use of such tightly controlled studies does, however, bring with it its own limitations. Provision of diet is a large undertaking and hence can limit subject numbers, length of the study design, and it does not reflect real-life practice. Isolating the dietary component under question from other elements within real food also presents a real challenge. For example, isolating gluten from other components of wheat such as amylase trypsin inhibitors and fructans is notoriously difficult.[98] The combination of results from these two approaches likely gives the best picture of mechanism of action as well as feasibility in real-life practice. Collaboration across research groups will improve access to resources required (eg, methodologies for food composition for dietary design; commercial kitchen facilities for provision of diet; access to sufficient numbers of patients; techniques for sample analysis such as microbial sequencing and metabolomics) to obtain results from multiple research approaches.

7.4 | Comparative therapies

Consideration should be given to what comparator groups to use within dietary studies. The low FODMAP diet and the NICE guidelines have been compared in three studies.[24,31,99] Another study assessing the low FODMAP diet created a "sham" diet which attempted to not alter other dietary constituents.[26] One study in quiescent IBD utilized a re-challenge protocol to assess symptom induction rather than symptom reduction through exclusion diet.[72] An alternative to the comparison of two dietary interventions is to compare two therapies, for example, diet and drug therapy or diet and psychological therapy.[100] The effect of gluten has been studied via use of blinded capsules containing placebo (rice starch),[37,40] through provided foods containing placebo (whey protein),[23] or via provision of gluten-free (maize and potato based) flours.[36] Gelatin capsules have been used as a placebo compared to capsaicin.[101] When designing placebo therapies, researchers should ensure it is unlikely to have effects on gastrointestinal symptoms or macronutrient intake. Ideally, randomized

TABLE 2 Proposed methods and current evidence for predicting response to dietary therapy

Pathophysiology	Biomarkers to predict response	Mechanisms, strengths, and limitations of the biomarker to predict response	Evidence of the biomarker to predict response to specific dietary therapies
Colonic fermentation creating gas	Hydrogen and methane breath testing	Measures colonic gas production as a bi-product of fermentation through expired air. The test is inexpensive and non-invasive. However, significant limitations exists due to poor reproducibility to both lactulose and fructose, and poor correlation with symptom induction to fructose challenge,[154] poor applicability of test doses to real-life consumption in the diet, and the risk of negative breath test results inappropriately steering patients away from dietary therapy.[155,156]	**Low FODMAP diet:** The highest response rate (81%) published for the low FODMAP diet in IBS patients was found in a study of 584 patients with known positive fructose and/or lactose intolerance (defined as malabsorption as well as symptom response on breath testing).[157] The high response rate suggests that the combination of positive breath and symptom response to fructose and lactose challenge may predict response. However, it is possible that the positive symptom response (as a measure of visceral hypersensitivity) as opposed to the positive breath hydrogen/methane result that is predictive of therapeutic gain.[155] Lactulose breath testing has been shown to be unsuccessful at predicting response to low FODMAP therapy.[28] **SIBO diet:** Breath testing for predicting response to SIBO treatment with diet is discordant, largely due to inability of breath testing to accurately identify the presence or absence of SIBO. Scintigraphy suggests measuring an early-rise in breath hydrogen following lactulose indicates oro-cecal transit as opposed to SIBO.[158] Additionally, variations within individuals following lactulose occur over time when using the early-rise in breath hydrogen criteria for SIBO.[154,159] The alternative of using glucose breath testing is also problematic as glucose is rapidly absorbed proximally in the small intestine. Additionally, sugar solutions have the ability to effect transit time.
	Magnetic resonance imaging (MRI)	Can be used to quantify gas and fluid within the lumen of the gastrointestinal tract as a measure of fermentation and osmotic fluid delivery. It's use as a non-invasive predictor of food-related symptoms may be beneficial, but this required further evaluation,[121] and may not be practical outside of the research setting secondary to cost.	**The low FODMAP diet:** Studies using MRI assessing symptom response have suggested visceral hypersensitivity defines symptom induction to FODMAP content of the diet, as opposed to the malabsorption itself.[121,160]
	Gas-sensing pills	New technology which enables real-time measurement of gastric gas and pH via a consumable capsule. Currently only utilized in animal models with carbon dioxide measurement.[161]	No studies in human dietary trials to date.
Nociception/visceral hypersensitivity	Rectal barostat	Rectal barostat is used for measurement of visceral hypersensitivity, but is invasive. Visceral hypersensitivity measured by rectal barostat has been shown seen in 50% of IBS patients, but hypersensitivity could not be predicted by biological biomarkers representing immune activation, neuroendocrine or microbial activity.[162]	**Low capsaicin diet:** IBS patients hypersensitive to rectal distention showed a significantly heightened perception of pain with capsaicin compared to non-hypersensitive IBS patients.[147]
Transit time	Wireless motility device measuring transit time	Measurement of alterations in gastrointestinal transit time may assist in understanding the role of diet in symptom genesis.	**Fiber supplementation:** A wireless motility device (SmartPill) showed colonic transit time and whole-gut transit time decreased with wheat bran supplementation.[163]
	High-resolution solid-state manometry	Measurement of gastric motility and accommodation	**Low FODMAP diet:** Fructans shown to induce higher postprandial gastric pressures compared to placebo (glucose) in healthy control and IBS patients.[123]

(Continues)

TABLE 2 (Continued)

Pathophysiology	Biomarkers to predict response	Mechanisms, strengths, and limitations of the biomarker to predict response	Evidence of the biomarker to predict response to specific dietary therapies
Alterations to the microbiota	Wireless motility device measuring pH	Alterations to diet may affect intracolonic pH via SCFA production, hence pH-sensing devices may be used as an indirect measure of ferementation.[164]	Whether this may be a helpful guide to predict response to therapies is unknown.
	Profiling of the fecal microbiota	Profiling the microbiota of fecal samples at baseline, prior to dietary modification, may provide non-invasive tool to predict response to dietary therapies. Microbiota of fecal samples can be analyzed via use of 16s rRNA sequencing. Novel technologies such as analysis through the "GA-map Dysbiosis Test" may be a useful tool in the future.[165]	**Low FODMAP diet:** Baseline gut microbiome composition and microbial metabolic capacity were shown to be associated with efficacy of the low FODMAP diet in a cross-over trial in 33 children with IBS using 16s rRNA sequencing.[58] Baseline measures showed that responders had greater microbes with saccharolytic capacity, such as *bacteroides*, *ruminococcaceae* and *dorea*, compared to non-responders. Non-responders had baseline bacteria that were less suited to fermentation of carbohydrates.[58] **Low FODMAP vs NICE diets:** In a study of adult IBS patients, using multivariate analysis, bacterial profiles measured by the GA-map Dysbiosis test differed between responders and non-responders for patients treated with the low FODMAP diet, but not with the NICE guidelines.[59] Of the 33 patients receiving low FODMAP dietary advice, total bacterial abundance tended to be greater in non-responders compared to responders both before and after dietary intervention.[59] *Bacteroides stercoris*, *Pseudomonas*, *Acinetobacter*, and the sulfur-reducing anaerobic genus *Desulfitispora* tended to be more abundant in the non-responding group.[59]
	Mucosal associated microbiota profiling	The "Brisbane Aseptic Biopsy Device" may provide insight into the effects of diet on the mucosa-associated profile.[166]	No studies in human dietary trials to date.
Immune activation	Metabolomic profiling	Metabolic profiling is increasingly being considered for determining the effect of diet through interaction with the microbiota and its bi-products.[167]	**Low FODMAP diet:** Histamine was reduced with the low FODMAP diet in IBS patients[28]
	Pro-inflammatory cytokines	Diet may induce a reduction in activity of inflammatory cells.	**Low FODMAP diet**: Pro-inflammatory cytokines IL-6 and IL-8 decreased on the low FODMAP diet compared to baseline.[60]
	Mucosal mast cells	It has been postulated that diet may modulate the microbiota resulting in harmful macromolecules, which may trigger release of mast cell mediators and active the immune system.[168]	**Lactose intolerance:** Lactose intolerance has shown to increase mucosal mast cells compared to those with lactose malabsorption in the absence of symptom response.[160] Higher mast cell count was found in patients with anxiety supporting the theory of neuro-immune modulation of visceral function effecting food intolerance.[160]
	Antigliadin antibodies	There is some suggestion that gluten can induce activation of innate immunity without causing detectable changes in barrier function,[98] and that antigliadin antibodies have been suggested as a potential predictor of response to a gluten-free diet.[169]	**Gluten-free diet:** In preliminary results of 45 IBS patients, 53% had positive antigliadin antibodies IgA or IgG, compared to 25% of 24 healthy controls. After 1-month of a gluten-free diet, those with positive antigliadin antibodies had improved constipation, diarrhea and abdominal pain, while those with negative antibodies only had improved pain. However, results were not dependent on compliance to the diet,[169] suggesting either strict adherence is not required, or effects were seen through other elements of the dietary change.

(Continues)

TABLE 2 (Continued)

Pathophysiology	Biomarkers to predict response	Mechanisms, strengths, and limitations of the biomarker to predict response	Evidence of the biomarker to predict response to specific dietary therapies
Confocal laser endomicroscopy	Epithelial (tight junctions) changes	This technique can identify subtle epithelial changes in response to acute exposure to foods and its application has been limited to common antigen mixtures of cow's milk, wheat, yeast, and soy. Identification of dietary proteins with positive reactions has been suggested to represent the cause of IBS.[170]	**Food antigens:** Exposure to suspected food antigens via endoscopy caused immediate breaks, increased intervillous spaces and increased intraepithelial lymphocytes in the intestinal mucosa in 22 of 36 patients with IBS and suspected food intolerance.[170] These changes were reported to be associated with symptom improvement following individualized exclusion diets based on results from the confocal laser endomicroscopy, with a >50% reduction in symptom score in 19 of the 22 patients.[170]
Genetic testing & nutrigenomics	HLA-DQ2 and HLA-DQ8	It has been proposed that patients carrying the genetic variants for celiac disease without mucosal lesions may be more likely to respond to a gluten-free diet,[141] although controversy exists due to the difficulty of adequate exclusion of celiac disease and difficulty in separating gluten from other components in the diet.	**Gluten-free diet:** In diarrhea predominant IBS patients, 60% responded to a 6-month gluten-free diet who expressed IgG and HLA-DQ2 compared to 12% who did not express the phenotype.[141] However, due to limitations in study design, and the nature of gluten in food, it is difficult to ascertain if the response was related to modification of gluten intake, or other components of the diet.
	Nutrigenomics	Personalized nutrition therapy based on genetic profiling shows potential for assisting in understanding and individuals susceptibility to disease and potential response to dietary intervention.[171,172]	No studies in dietary trials with IBS patients to date.
	Tryptophan hydroxylase 1	Tryptophan hydroxylase 1 is involved in serotonin signaling, which has been implicated in IBS pathogenesis.[173]	**Low FODMAP diet**: Tryptophan hydroxylase 1 genetic variants may also have the ability to predict response to the low FODMAP diet.[174]
Other	Volatile organic compounds	An inexpensive, non-invasive biomarker measured in fecal samples with preliminary data available for potential use to predict response to dietary therapy.	**Low FODMAP diet:** Preliminary data suggest that volatile organic compounds may assist to predict response to therapy.[175]

FODMAP denotes fermentable oligo- di- mono-saccharides and polyols; IBS denotes irritable bowel syndrome; MRI denotes magnetic resonance imaging; NICE diet denotes National Institute for Clinical Excellence diet; SIBO denotes small intestinal bacterial overgrowth.

double-blind, placebo-controlled trials are utilized to reduce both the placebo and nocebo effect and provide the highest quality of evidence possible. In light of the above options used for comparative therapies, researchers must consider which is best able to be performed with the resources available, ensure adequate blinding, and include defined baseline periods to quantify habitual intake of the food component in question.[21] Keeping in mind that methodologies for dietary trials are unlikely to meet the stringent criteria used in pharmacotherapy.[21]

7.5 | Blinding

Blinding participants is one of the greatest challenges of performing dietary studies. In the modern era, whereby access to health information, especially related to diet is easily accessible and readily discussed in the media, recruitment of diet-naive patients is near impossible. Criticism of the low FODMAP diet has suggested that the efficacy of the diet has been driven by the placebo effect secondary to large risk of bias.[33] However, as discussed by Gibson et al it is healthy controls, who should be unable to successfully distinguish dietary therapies based on symptomatic response, who may assist in evaluating the success of blinding.[102]

7.6 | Compliance

Monitoring of dietary intake throughout studies presents another challenge. Underreporting of total energy intake in food records can range from 11.9% to 44%.[103] In addition to underreporting, participants are likely to alter their dietary intake during the food record period.[103]

8 | FUTURE DIETARY RESEARCH—KEY RESEARCH QUESTIONS

8.1 | Efficacy

As highlighted in Table 1, many of the existing dietary modifications currently lack supporting evidence of efficacy. Due to the potential for serious adverse health effects through the use of diet, all diets should undergo rigorous evaluation as per Figure 1 prior to widespread use. The potential for high placebo response rates in patients with functional symptoms should be considered as well as whether the patients' will-to-succeed with dietary therapy in preference to drug therapy may improve efficacy and/or compliance. Initial improvement in patients' symptoms as a result of placebo effect may then see a return of symptoms, at which time the patient seeks the next dietary therapy, leading to accumulation of dietary restrictions and increasing adverse health effects. Long-term (>6-12 months) symptom improvement suggests therapeutic efficacy as opposed to placebo response, as has been shown with the use of the low FODMAP diet in IBS.[50,51,100]

8.2 | Predictors of response

As discussed above and in Table 2, ability to predict response would allow for practitioners to target dietary therapies to the individual and modify the dietary recommendations accordingly.

8.3 | Mechanisms of action

Understanding mechanisms of action of any given dietary therapy could advance knowledge in several ways. Firstly, identifying mechanistic pathways gives rise to opportunities to identify ways to predict response. Secondly, through improved understanding of mechanisms of action, diet has potential to enhance knowledge of pathophysiology of disease. The tools listed in Table 2 highlight the growing array of techniques available to study mechanisms of action.

8.4 | Level of dietary restriction required

Due to the potential harmful effects of using restrictive diets, limiting the level of restriction utilized in exclusion diets would be ideal. However, proof-of-concept studies are generally designed to maximize differences between diets in order to ensure an effect is seen (if there is one). Hence, it then becomes a secondary question as to what level of restriction is necessary. The FODMAP intake achieved upon institution of the low FODMAP diet has varied between clinical trials, with dietary education-based trials achieving an average FODMAP intake of 10-12 g/day[26,51] compared to 3 g/day provided in a feeding study.[30] Despite this, similar improvements in symptoms were reported, suggesting the level of restriction need not be too stringent. Clinical practice also indicates that tolerance to food components is variable between individuals, and it is likely that many individuals would have an adequate response to a modified version or less-restrictive version of many of the diets, but how this can be predicted is not known.

8.5 | Duration of therapy

An important part of the development of any dietary strategy is assessing the length of time patients are required to follow the diet

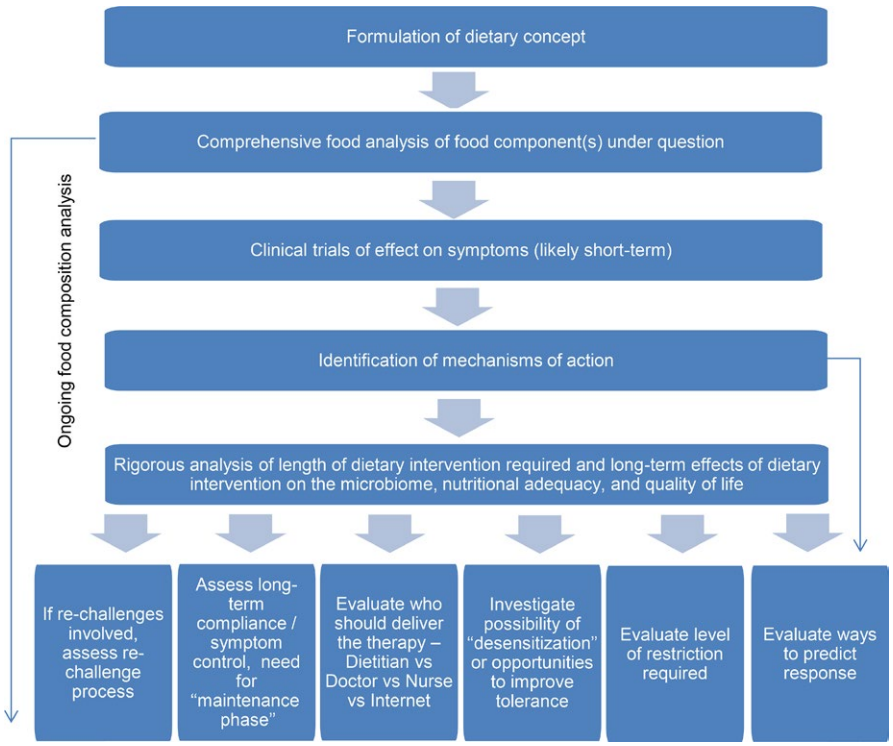

FIGURE 1 Flow chart for the evaluation of dietary concepts for gastrointestinal conditions

and what happens thereafter. In designing research studies, consideration should be given to the proposed mechanism of action, as some dietary components thought to have subtle long-term effects (eg, manifestations of inflammation) may require longer study protocols.[34] It is thought that symptoms should usually resolve after 3-4 weeks on an exclusion diet,[104] but this should be clearly defined and communicated for each dietary therapy following thorough investigation, to ensure restrictive diets are not used for longer than necessary. A re-challenge protocol has been published for the low FODMAP diet largely based on clinical experience,[105] and a small number of trials recently published.[50,51,72] In IBS patients, FODMAP intake was reduced to 36% of usual intake during the restrictive phase, but increased to 79% of usual intake following re-challenge.[51] While another study found 82% followed an adapted low FODMAP diet (FODMAP intake 21 g/day) vs 18% who returned to a habitual diet (FODMAP intake 29 g/day, $P = .039$) at long-term follow-up.[50] This suggests that most patients are able to re-introduce significant amounts of FODMAPs back into the diet and maintain symptom control in the longer term. Re-challenge protocols for other dietary therapies are poorly described, potentially leading to patients remaining on a restrictive diet for long periods due to lack of further guidance. Following the re-challenge phase, a long-term "maintenance phase" or "adapted diet" may be encouraged to ensure continued symptom control.

8.6 | Improving food tolerance

Once a dietary therapy is established, ways to improve tolerance to the dietary component should be investigated. If the dietary component can be identified as problematic in an individual, a subsequent therapy can then be targeted to improve tolerance to the food component with the aim to allow liberalization of the diet and improved nutritional adequacy. This may be in one of two ways, targeted therapy to use at the time-of-consumption or more longer term strategies. Symptoms in IBS patients have been improved with enzyme substitution with α-galactosidase when targeted specifically to foods high in galacto-oligosaccharides.[106] These promising results were in contrast to previous studies showing no effect of the enzyme when poorly targeted to dietary galacto-oligosaccharides.[107] Enzyme supplementation therapy may also be a therapeutic target for sucrose-isomaltase deficiency, although few studies exist.[108] The importance of studying the effect of such targeted therapies in the correct population group was highlighted when additional glucose was unable to improve gastrointestinal tolerance to excess fructose in FBD patients despite reduced gas production[109] and physiological mechanisms suggesting it would.[110]

The second way to improve tolerance is more relevant to a longer term scenario. For example, TRPV1 desensitization improved capsaicin tolerance following 5-6 weeks of exposure to 2.5 g/day of red pepper powder.[111] Another example is adaptation of the microbiota by gradual and frequent re-introduction of the food component to modulate the microbiota in a favorable manner to improve food tolerance. Introduction of 3.5 or 7 g trans-galacto-oligosaccharide for 12 weeks in IBS patients enhanced fecal *Bifidobacteria* and improved gastrointestinal symptom scores, with the higher dosage also improving subjective global assessment and anxiety scores.[112] It is possible that restriction of a food component for a period of time may worsen overall tolerance to that food component. This phenomenon is often expressed by patients utilizing dietary therapy. It is unclear if this is related to patient perception, with enhanced awareness of symptoms upon re-introduction. Alternatively, the microbiota may have modified in response to dietary change in a less-favorable way to reduce tolerance. Lastly, future research may consider the possibility of utilizing dietary fiber supplements to modulate or reduce bile acids[113] which may be implicated in the pathophysiology of IBS.[114]

9 | CONCLUSIONS

While dietary therapy has a lot to offer patients with FBD, there are many unanswered questions. The low FODMAP diet has received the most attention recently and as a result there is growing evidence about its efficacy, side-effects and potential ways to predict response. However, many other dietary therapies offer potential to assist patients with FBD, but require further elucidation prior to widespread use. An important area for future research is the ability to predict response to dietary therapies and allow individualized therapy. The search for biomarkers to predict response offers a unique opportunity for diet to further our understanding of mechanisms of disease.

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CONFLICTS OF INTEREST

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