



Microbiota-Based Biomarkers in Irritable Bowel Syndrome: Evidence, Limitations, and Translational Readiness

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ABSTRACT

Irritable bowel syndrome (IBS), which is now classified as disorders of gut-brain interaction, is diagnosed mainly through the symptom-based Rome criteria. While gut microbiota dysbiosis has been repeatedly linked to IBS pathophysiology, no reproducible microbiota based diagnostic signature has been established yet for universal clinical application. This mini review critically evaluates microbiota associated biomarker research in IBS studies, distinguishing discovery stage microbial associations from clinically relevant biomarkers. Evidence was assessed across taxonomic signatures, microbiome diversity measurements, short-chain fatty acids, bile acid metabolism, tryptophan related metabolites, immune-associated markers, and multi-omics approaches. Current findings suggest that taxonomic markers alone remain inconsistent and greatly impacted by cohort, diet, geography, sequencing method, and analytical pipeline. Functional and multi-marker approaches, specifically the integration of metabolomic and host-response data appear more mechanistically plausible but remain limited by small cohorts, cross-sectional designs, incomplete external validation and lack of methodological standardisation. Commercial and research profiling platforms including dysbiosis testing approaches showcase translational potential but should not yet be considered validated diagnostic replacements for the Rome based clinical diagnosis. Overall, microbiota-based biomarkers are best understood as potential future adjuncts for patient stratification, mechanism-based subtyping, and treatment response prediction rather than singular diagnostic tools. Progress towards clinical implementation will need longitudinal, multi-center, standardised, and externally validated studies supporting the integration of microbial composition, function, individual host factors and patient level clinical data for adequate application

Keywords: gut-microbiota, irritable bowel syndrome, biomarkers, metabolomics, gut-brain axis

INTRODUCTION

Functional gastrointestinal disorders (FGIDs) are classified under the Rome IV criteria as symptom-based disorders lacking structural pathology. Diagnosis depends on clinical symptoms, such as abdominal pain, altered bowel habits, and bloating (Schmulson & Drossman, 2017; Lacy & Patel, 2017). FGIDs are also titled disorders of gut-brain

interactions (DGBIs). Although microbiota alterations have been demonstrated across several DGBIs, this mini review focuses mainly on IBS because it has the most developed microbiota-biomarker literature and the strongest body of human cohort evidence. Approximately 30–40% of individuals worldwide report FGIDs, especially IBS, which constitutes about 10–15% of the cases globally (Sperber et al., 2021). This prevalence creates a significant clinical burden for affected individuals and healthcare systems including reduced quality of life and increased healthcare costs (Black et al., 2020). A key limitation of current IBS management is the lack of validated biological markers for objective subtyping, prognosis, and treatment-response prediction. Symptom overlaps frequently occur among FGIDs. Although Rome-based diagnosis can be made positively in appropriate clinical contexts, the absence of clinically validated biological markers limits objective subtyping, prognosis and treatment response prediction. Despite these limits, emerging research links gut microbiota dysbiosis to IBS pathogenesis. This is shown through metagenomic sequencing and promising metabolomics data (Chen et al., 2021; Wei et al., 2021; Chong et al., 2019; Kraimi et al., 2024; Saleem et al., 2025). Microbiota-based biomarkers can be categorised into taxonomic, metabolic, and immune-associated biomarkers. Taxonomic biomarkers demonstrate the differences in the relative abundance of microbial groups while functional and metabolomic biomarkers assess microbial pathways, metabolites, and host-microbe interactions. The immune-associated level highlights host further interactions with the gut microbiota (Gebrayel et al., 2022). To contextualise the limitations of the current symptom-based

diagnostic frameworks and highlight the need for objective biomarkers, a comparison between current and emerging methods of diagnosis is summarised in Table 1. This mini review critically assesses the current literature on these emerging topics. It will also evaluate the prognostic and diagnostic potential of biomarkers in clinical settings and analyse translational challenges.

LITERATURE SEARCH STRATEGY

This mini review was based on a targeted literature search for PubMed/MEDLINE, Scopus, and Google Scholar for studies and reviews addressing microbiota-associated biomarkers in irritable bowel syndrome and related disorders of gut-brain interactions. Search terms included combinations of “irritable bowel syndrome”, “IBS”, “functional gastrointestinal disorders”, “disorders of gut-brain interactions”, “microbiota”, “microbiome”, “dysbiosis”, “biomarker”, “metabolomics”, “short-chain fatty acids”, “bile acids”, “tryptophan metabolism”, “immune markers”, “cytokines”, and “multi-omics studies”. Priority was given to human IBS studies, systematic reviews, multi-omics studies, metabolomic studies, and papers addressing translational or diagnostic importance. Mechanistic studies such as animal or non-IBS studies were only used to clarify biological pathways rather than as direct evidence of clinical biomarker validity. Studies were interpreted in a narrative manner rather than quantitatively due to the heterogeneity in diagnostic criteria, sample type, sequencing platform, analytical pipeline and reported outcomes. Searches focused primarily on studies published from 2016 to 2026, with older landmark mechanistic papers included where relevant.

Table 1. Comparison of the current Rome IV symptom-based diagnostic framework and emerging microbiota-based biomarker approaches for IBS. The Rome IV framework remains the established clinical standard (Schmulson & Drossman, 2017; Lacy & Patel, 2017), whereas microbiota-based biomarkers are currently considered research-stage adjuncts that require further external validation before routine clinical implementation (Pittayanon et al., 2019; Gebrayel et al., 2022; Tegegne & Savidge, 2025).

Feature	Current Approach (Rome IV Criteria)	Microbiota-Based Biomarkers (Emerging)
Current role	Primary clinical diagnostic framework	Research-stage adjunctive tools
Main strength	Standardised symptom-based classification	Biological insight into mechanisms
Main limitation	Limited biological stratification	Heterogeneous, non-standardised, not externally validated
Clinical utility	Diagnosis and clinical management	Mechanistic research, stratification hypothesis
Clinical readiness	Fully established clinical framework	Mostly at the discovery/translational stage
Risk of overuse	May not completely capture biological heterogeneity	May overinterpret non-specific dysbiosis

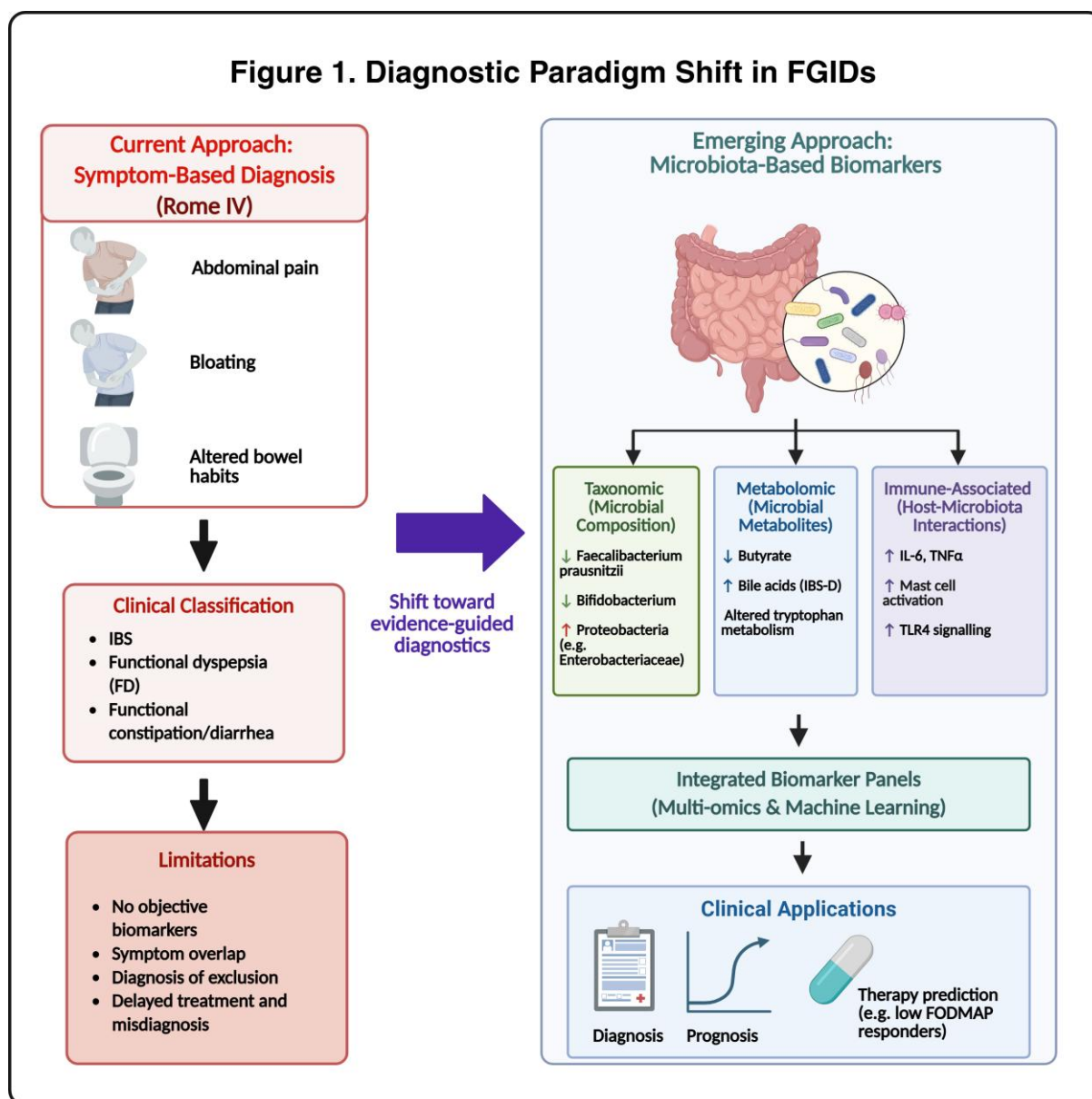


Figure 1 Potential framework for microbiota-associated biomarkers in FGIDs, particularly IBS. Rome-based criteria remain in the primary clinical diagnostic framework while microbiota based taxonomic metabolomic and immune markers are currently best understood as research stage adjuncts or future patient stratification.

PATHOPHYSIOLOGICAL BASIS OF IBS WITHIN DISORDERS OF GUT-BRAIN INTERACTION

Gut-Brain Axis Dysregulation

The Gut-brain axis comprises a major pathophysiological pathway of IBS. The gut-brain axis is a bidirectional signalling mechanism between the central nervous system (CNS), the enteric nervous system (ENS), the immune system, endocrine pathways, and the gut (Mayer et al., 2023; Liu et al., 2022; O'riordan et al., 2025). This axis operates through varying communication pathways. The neural pathway includes vagus nerve signalling. Furthermore, the endocrine system includes the hypothalamic-

pituitary-adrenal (HPA) axis, which regulates cortisol levels. And the immune pathway operates through the production of cytokines, particularly IL-6 and TNF- α (Ng et al., 2018; Schirmer et al., 2017). The gut microbiota has been shown to affect several hormonal pathways through the gut-brain axis, including serotonin, which is produced primarily in the gut (Gao et al., 2020). Microbial metabolites including SCFAs and tryptophan derivative may influence enteroendocrine, immune and neural signalling pathways relevant to visceral sensitivity (Silva et al., 2020). Although microbiota-mediated neurotransmitter modulation has been studied widely in

neuropsychiatric contexts its relevance to IBS biomarker development remains indirect and should be interpreted cautiously (Ahmed et al., 2022; Alli et al., 2022; Zhou et al., 2023). This influence has great mechanistic implications, as these dependencies were linked to altered stress responses, increased visceral hypersensitivity, and pain amplification (Strandwitz, 2019). Overall, the gut-brain axis provides biological plausibility for microbiota associated biomarkers in

IBS; however, mechanistic evidence remains heterogenous. Microbial metabolites may influence enteroendocrine signalling, immune activation, epithelial barrier function, vagal pathways, and visceral sensitivity. However, much of the causal evidence comes from preclinical models, while human IBS studies remain largely associative. Therefore, gut brain axis mechanisms should be used to support plausibility not to claim validated diagnostic utility.

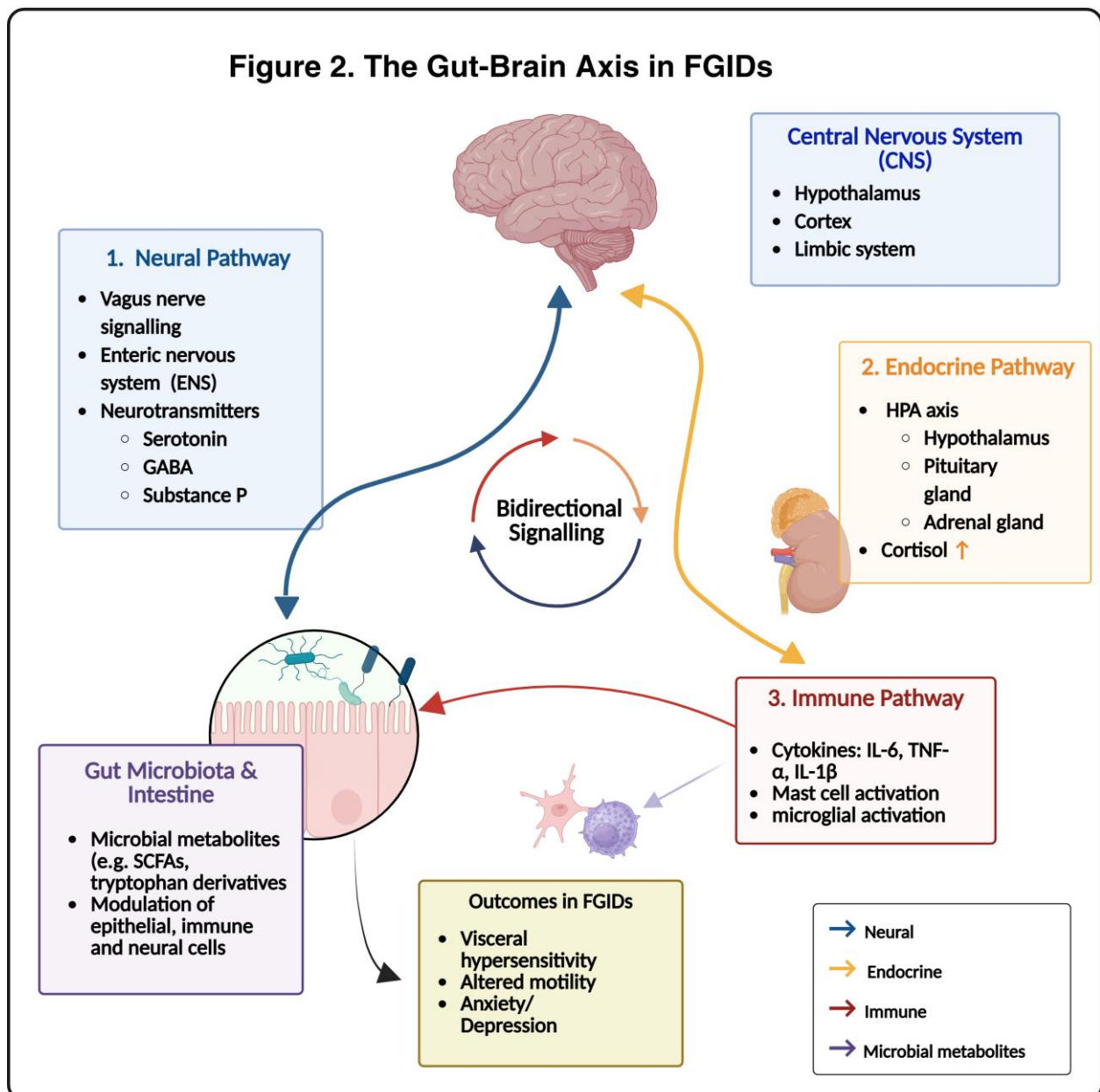


Figure 2 Overview of the gut–brain axis in FGIDs, particularly IBS. Bidirectional communication occurs via neural (vagus nerve), endocrine (HPA axis), and immune (cytokine-mediated) pathways. Gut microbiota influence neurotransmitter production and stress responses through microbial metabolites such as SCFAs and tryptophan derivatives, providing biological plausibility for symptom generation and biomarker discovery, although most human evidence remains associative.

Intestinal Barrier Dysfunction and Epithelial Integrity

Intestinal barrier dysfunction has been reported in subsets of IBS and other DGBIs. The intestinal barrier structure, comprising a single epithelial layer, can be affected by gut microbiota dysbiosis, causing its tight junction proteins, particularly occludin, claudins and zonula occludens-1 (ZO-1), to become “leaky” due to increased permeability (Arumugam et al., 2024; Kumar et al., 2022; Martínez-Sánchez et al., 2022). This allows microbial antigens to cross the barrier, triggering immune activation. Additionally, reduced availability of barrier-supportive microbial metabolites, particularly, butyrate may contribute to impaired epithelial integrity. However, stool SCFA concentrations are influenced by diet absorption, transit time and sample handling so they should not be interpreted as direct evidence of barrier dysfunction without complementary functional data (Singh et al., 2019). Current evidence includes increased permeability observed in IBS-D patients and a correlation with symptom severity (Barbara et al., 2021).

Immune Activation and Low-Grade Inflammation

While FGIDs classification does not include overt inflammation, low-grade inflammation has been evidenced in recent studies. The mechanistic pathway involves increased mast cell numbers and T-cell activation in IBS patient samples (Vanuytsel et al., 2023). Furthermore, cytokine alterations were also evident in some studies, including elevated levels of IL-6 and TNF- α , suggesting a low-grade pro-inflammatory immune activation (Schirmer et al., 2017; Ng et al., 2018). Potential microbial triggers include bacterial components that activate Toll-like receptors and other pattern-recognition receptor pathways (Shi et al., 2017). The outcomes of these studies show links between IBS symptoms and chronic low-grade inflammation, as well as increased neuronal sensitisation (Zhao et al., 2025).

Altered Gastrointestinal Motility and Visceral Hypersensitivity

Visceral hypersensitivity accounts for an increased pain response to normal stimuli, while motility changes account for changes in intestinal transit. Motility changes in IBS are particularly prevalent in recent studies; IBS-D was associated with accelerated transit, while IBS-C was associated with delayed transit (Dimidi et al., 2017). This further highlights the

microbial influence on these pathophysiological pathways, as SCFAs and other fermentation products can influence their motility, secretion and gas production, but their effects are dependant on concentration, site of production, bowel habit subtype, diet and transit time (Van Der Hee & Wells, 2021). These findings support a biologically plausible link between microbiota-derived metabolites, ENS modulation, altered motility, and visceral sensitivity (Singh et al., 2022).

GUT MICROBIOTA AND HOST-MICROBE INTERACTION IN FGIDS WITH EMPHASIS ON IBS

Composition and Functional Role of the Gut Microbiota

The composition of gut microbiota, particularly at the taxonomic level, has been profiled in many studies; the dominant phyla include Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria (Pasolli et al., 2019). Their functions and interactions are essential for homeostatic modulation. Digestion is modulated through fibre fermentation levels. Functional capacity varies greatly below the phylum level; therefore, broad-phylum-level description cannot reliably predict SCFA production, inflammatory potential or clinical phenotype. Species and strain level resolution, functional metagenomics, metabolomics or absolute abundance data are needed to infer biological activity (De Filippis et al., 2020). Immune regulation and barrier maintenance, as highlighted by the aforementioned mechanistic pathways, are also dependent on the dominant gut flora (Wang et al., 2023).

Dysbiosis and Microbial Imbalance in IBS

Dysbiosis refers to an altered microbial community structure or function typically ascertained by analysing alpha and beta diversity, relative to a comparison group, but it is not a single standardised diagnostic state. analysing alpha and beta diversity levels. Alpha diversity of gut flora accounts for within sample diversity, typically reflecting richness or evenness or both depending on the index used. Beta diversity accounts for between-sample differences in community composition at a chosen taxonomic/feature level (Pittayanon et al., 2019). These measurements are useful for ecological indicators but are not disease-specific biomarkers on their own. In IBS, reported alpha-diversity findings are inconsistent with some studies demonstrating lowered diversity and other showcasing no significant

difference. Beta-diversity clustering could potentially indicate group level compositional differences but overlap between IBS and control samples limits its diagnostic applicability (Wei et al., 2021). Common findings further include lower levels of *Bifidobacterium* and *Lactobacillus* and increased levels of Proteobacteria-associated taxa (Chong et al., 2019; Saleem et al., 2025). However, despite these findings, a global standard has yet to be set, as they are population-specific and diet-dependent (Malesza et al., 2021). The key limitation remains that currently no universal microbial signatures are available.

Microbiota-Mediated Modulation of the Gut-Brain Axis

Microbial metabolites may influence gut-brain signalling through enteroendocrine, immune, vagal, and stress-response pathways. However, evidence from neuropsychiatric or preclinical studies should be used only to support mechanistic plausibility, not as direct evidence of IBS biomarker validity (Gao et al., 2020). Vagal signalling modulation also hinges on microbial metabolites, as evidenced by recent findings (Strandwitz, 2019). This can lead to behavioural and psychological effects such as increased levels of anxiety, stress and depression. Current research continues to assess the prevalent link between gut-microbiota profiles and such psychological disorders, highlighting promising avenues in personalised treatments through the management of gut dysbiosis (Kraimi et al., 2024).

MICROBIAL TAXONOMIC SIGNATURES AS CANDIDATE BIOMARKERS

Alterations in Microbial Diversity

Variations in gut flora have been profiled in several studies, providing potential evidence for the use of microbiota-based biomarkers. Reduced alpha diversity has been reported in some IBS cohorts, but findings are inconsistent across studies. Some studies report lower Shannon diversity in IBS, but this does not define a reproducible clinical threshold and may reflect differences in richness, evenness and sampling (Tap et al., 2017). This provides multiple mechanistic interpretations, particularly that lower microbial taxonomic diversity links to reduced ecosystem resilience and thus increases susceptibility to perturbations, such as varying diets and antibiotics. Additionally, a distinct clustering was profiled for the beta diversity in IBS cohorts. This highlighted group-level beta-diversity differences between IBS and control cohorts. However, this clustering can be

considered weak or overlapping due to variations. This highlights the critical limitation of diversity profiling: studies do not show consistent diversity thresholds that define specific IBS subtypes, and they also show high inter-individual variability.

Taxonomic Shifts Associated with IBS Phenotypes

Next, the common but inconsistent patterns across taxonomic data studies were dissected. According to these studies, several IBS cohorts showed a decreased relative abundance of Firmicutes, especially butyrate producers such as *Faecalibacterium prausnitzii*, as well as *bifidobacterium* and *lactobacillus*, with increased relative abundance of Proteobacteria-associated taxa that may include pro-inflammatory members (Pittayanon et al., 2019). However, broad phylum-level shifts cannot be used to infer metabolite production or endotoxin exposure without functional, metabolomic, or absolute abundance data. While these studies may intersect slightly, taxonomy alone is insufficient evidence as it must directly link to function. This is missing from current research, as microbial shifts vary significantly across assessed cohorts and no reproducible IBS specific microbial signature has been validated for routine clinical application; this is a critical limitation evident in the current literature.

Microbial Profiles Across Irritable Bowel Syndrome Subtypes

IBS is commonly subtyped by predominant bowel habits, including IBS-D, IBS-C, IBS-M, and IBS-U. In which IBS-D, IBS-C, and IBS-M are more commonly represented in biomarker studies than IBS-U. IBS-D has been associated in some studies with altered bile-acid metabolism, increased relative abundance of Proteobacteria-associated taxa and reduced relative abundance of selected butyrate-producing taxa; however, these associations are not consistent enough to define IBS-D diagnostically. IBS-C profiles have been associated with increased levels of methane production and a higher abundance of methanogenic archaea such as *Methanobrevibacter smithii*, which slows intestinal transit and therefore may contribute to slower intestinal transit in some patients. IBS-M is considered highly variable in nature due to its diarrheal and constipation symptomatic onset, and so it has the weakest biomarker reliability. The key issue is that subtype classification is not always standardised, and studies do not stratify it properly, reducing causal links (Mars et al., 2020).

MICROBIAL FUNCTIONAL AND METABOLOMIC BIOMARKERS

Short-Chain Fatty Acid Profiles and Metabolic Signalling

The main SCFAs produced by microbial fermentation in the human colon are acetate, propionate and butyrate. These are produced via the fermentation of dietary fibre and so are essential in digestive mechanisms as highlighted in the general pathway in Figure 3. Butyrate is one of the most studied SCFAs and provides 70-80% of colonocytes' energy requirements. Furthermore, it acts as a main modulator of tight junction regulation (Martin-Gallausiaux et al., 2020). These functions combine to

confer anti-inflammatory properties through its role as a histone deacetylase inhibitor. As an HDAC inhibitor, it increases the expression of anti-inflammatory genes and regulates epithelial barrier genes, thereby linking to its aforementioned functions. Findings from IBS cohort studies support this, as reduced butyrate producers were observed; on the other hand, metabolite levels varied across studies. Therefore, reduced relative abundance of known butyrate-producing taxa may suggest altered fermentative potential; but stool SCFA levels are influenced by diet, absorption, transit time, and sample handling. Therefore, SCFAs are mechanistically plausible but not independently validated as IBS diagnostic biomarkers.

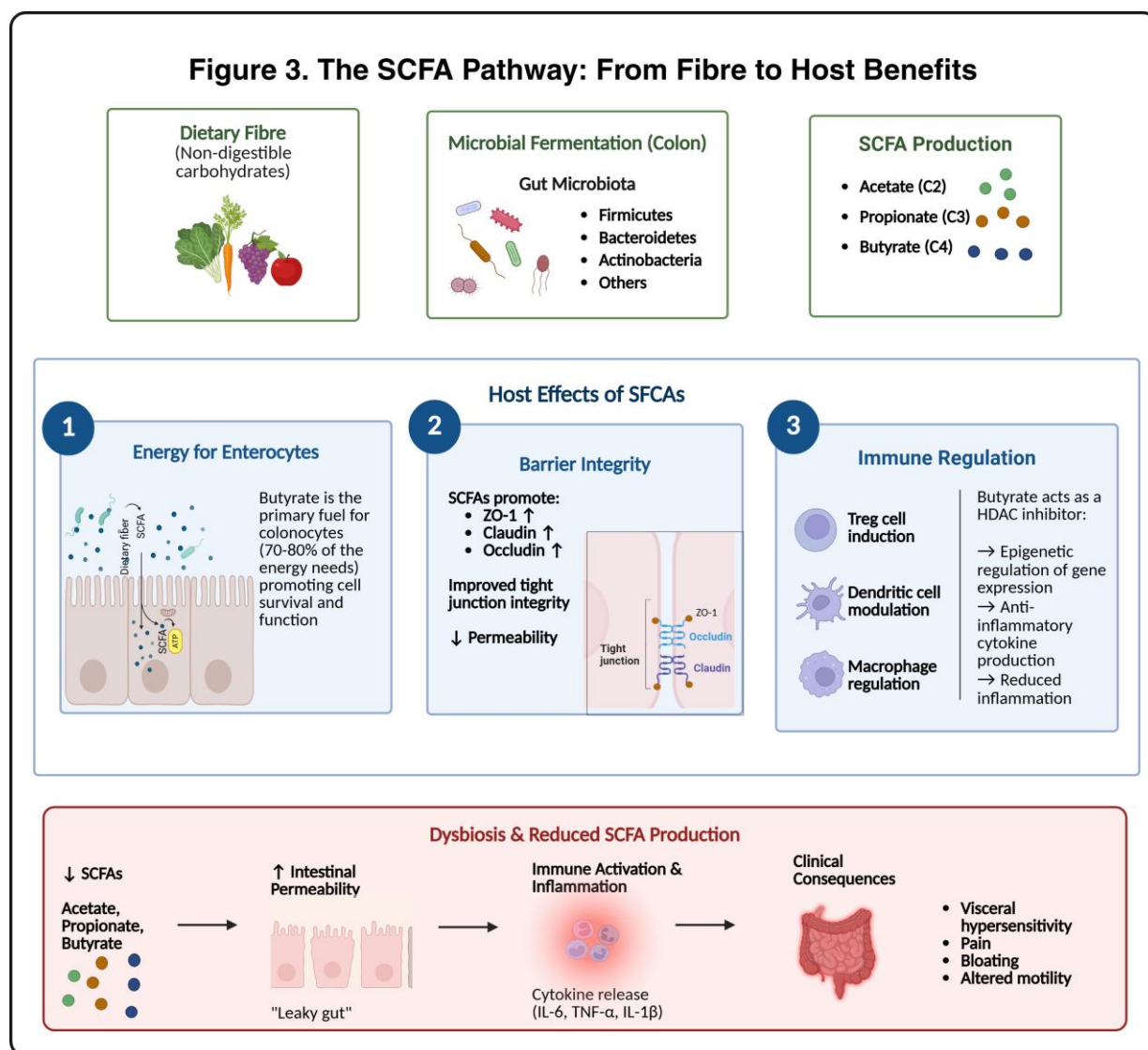


Figure 3 Microbial fermentation of dietary fibre produces short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate. These metabolites regulate intestinal barrier integrity, provide energy for colonocytes and modulate immune responses by epigenetic mechanisms such as histone deacetylase (HDAC) inhibition. Dysbiosis associated reductions in SCFA production may contribute to barrier dysfunction and inflammation but direct validation is required.

Microbial Metabolism of Bile Acids and Host Signalling Pathways

The bile acid metabolism has clear interactions with host signalling pathways. Microbiota also play an essential role in its maintenance, acting as a modulator by converting primary bile acids into secondary bile acids. In subsets of IBS-D, increased colonic bile acid exposure or bile acid malabsorption has been reported, whereas altered bile-acid availability may contribute to constipation-predominant symptoms in selected patients. This highlights the mechanisms underlying bile acid production, which regulate motility and fluid secretion (Guzior & Quinn, 2021). These levels of bile acid production yielded potential profiles, offering adjunct options for functional biomarkers. However, while bile acid metabolism is clinically relevant to IBS-D because bile acids influence intestinal secretion and motility, bile profiles are still affected by hepatic synthesis, enterohepatic circulation, diet, transit time, and host metabolism. Therefore, bile acid-related markers may be useful for mechanistic subtyping in selected patients but should not be presented as universal IBS biomarkers.

Tryptophan Metabolism and Neuroactive Microbial Metabolites

Neuroactive microbial metabolites remain under-researched in the current literature and are implicated in microbial tryptophan metabolism, which produces indole derivatives and serotonin precursors (Gao et al., 2020). Serotonin regulates gut motility and affects pain perception through the tryptophan metabolism. Evidence in IBS remains limited and heterogeneous; therefore, tryptophan-related metabolites should be presented as mechanistically plausible candidate markers rather than validated diagnostic biomarkers.

INFLAMMATORY AND IMMUNE-ASSOCIATED MICROBIOTA SIGNATURES

Microbiota-Induced Immune Modulation

Immune modulation is another associated mechanism with microbiota signatures. Microbial metabolites and structural components can interact with dendritic cells, epithelial cells, and pattern-recognition receptors, thereby influencing T-cell differentiation, including regulatory T-cell responses. This interaction further promotes immune tolerance. Bacterial components such as LPS may activate Toll-like receptor pathways, including TLR4-mediated signalling (Shi et al., 2017). This results in pro-inflammatory signalling.

Cytokine and Inflammatory Marker Associations

Cytokine profiles also vary depending on microbiota signatures. Observed changes include increased levels of IL-6 and TNF- α as well as an altered IL-10 balance (Schirmer et al., 2017). This links these mechanistic pathways to increased cytokine production, highlighting the resulting visceral hypersensitivity. It can therefore be concluded from the findings that immune markers may provide complementary host-response driven information however they are not specific to microbiota driven IBS and overlap significantly with infection, inflammation, stress, diet and other gastrointestinal disorders.

Microbial Contributions to Intestinal Immune Dysregulation

Chronic low-grade inflammation is a leading factor in immune dysregulation, due to persistent immune activation (Ng et al., 2018; Vanuytsel et al., 2023). In IBS and other DGBIs, immune activation is generally low-grade and does not resemble the overt mucosal inflammation characteristic of IBD. Furthermore, microbial metabolites can regulate immune gene expression, highlighting additional epigenetic mechanisms. Particularly due to changes in immune cells resulting from DNA methylation. The limitation, however, remains with the difficulty of distinguishing correlation from causality, which is missing from the current literature.

MULTI-OMICS APPROACHES IN BIOMARKER DISCOVERY

Metagenomic and Sequencing Technologies in Microbiome Research

Sequencing technologies have been steadily developing, with the most commonly used technology for microbiota profiling being 16S rRNA, which provides community-level taxonomic profiling, often to genus-level resolution depending on the amplified region and reference database; however, it cannot assess function or interactions (Wensel et al., 2022). On the other hand, shotgun metagenomics provides higher taxonomic resolution and functional potential, although it does not directly measure gene expression or metabolite activity, though its costs are much higher than those of 16S rRNA, limiting its research applications. Despite that, functional profiling may be more informative than taxonomy alone, particularly when paired with metabolomic and host-response data.

Integration of Multi-Omics Data in Biomarker Identification

Multi-Omics have provided promising avenues for biomarker identification, combining the microbiome, metabolome, and transcriptome in their data, thereby linking microbial presence to function and host response, yielding useful and informative data. This integration assesses function over composition, an important consideration in developing biomarker identification mechanisms (Mars et al., 2020). Furthermore, computational modelling may eventually support the integration of microbiome, metabolomic, immune, and clinical data for IBS patient stratification. However, current microbiome datasets are often limited by small sample sizes, high feature-to-sample ratios, cohort heterogeneity, and incomplete external validation. Therefore, machine-learning approaches should be viewed as exploratory tools for biomarker discovery rather than clinically validated diagnostic models (Tegegne & Savidge, 2025).

CLINICAL UTILITY AND TRANSLATIONAL POTENTIAL

Diagnostic and Prognostic Applications

Diagnostic applications still require clinically approved microbiome diagnostics for IBS due to lack of causal relationships in the current literature for universal signatures; this appears to be difficult. However, if such gaps are filled, this could provide many diagnostic and prognostic applications, including stool-based microbiome tests that are in development (Gebrayel et al., 2022; Tegegne & Savidge, 2025). One translationally relevant example is the GA-map™ dysbiosis test, used in an IBS study combining faecal microbiota profiling with GC-MS/MS metabolomics. In that study, microbiota and metabolite profiles separated IBS patients from healthy subjects, with metabolites acting as the main driver of separation. The intestinal microenvironment profile also differed between IBS-C and IBS-D but did not clearly cluster by symptom severity or anxiety (Ahluwalia et al., 2021).

Table 2. Summary of microbiota-associated biomarker approaches and their current translational readiness based on evidence from microbiome profiling, sequencing technologies, metabolomics, and multi-omics integration (Mars et al., 2020; Wensel et al., 2022; Gebrayel et al., 2022; Tegegne & Savidge, 2025).

Approach	Measurement	Current research use	Translational Strengths	Limitations	Clinical Readiness
16S rRNA sequencing	Relative abundance of bacterial taxa	Exploratory profiling of microbial community structure in IBS cohorts	Commonly used, cost-effective	Limited functional information affected by primer choice, sequencing region, DNA extraction and analytical pipeline, not diagnostic on its own	Discovery-stage
Shotgun metagenomics	Higher-resolution taxonomic profiling and microbial functional potential	Identification of microbial genes and pathways that may relate to IBS subtypes	Provides more functional information than 16S sequencing	Expensive and computationally complex; measures functional potential rather than metabolite activity	Translational research-stage
Metabolomics (SCFAs)	Microbial metabolites and host – microbe interactions	Candidate marker discovery for mechanistic subtyping	More directly linked to microbial function and host physiology than taxonomy alone	Strongly influenced by diet, transit time, sample handling, host metabolism and analytical platform	Translational research-stage
Cytokine profiling	Immune markers (IL-6, TNF α , IL-10)	Complementary host-response information that may support mechanistic stratification	Captures host immune activity	Not specific to microbiota-driven IBS; overlaps with infection inflammation, stress, diet and other factors	Experimental adjunctive marker
Multi-omics	Combination of microbiome, metabolome, and host data	Integrative biomarker discovery and future patient stratification	Most informative research framework but complex and unvalidated clinically	Requires large cohorts, harmonized protocols, advanced analysis, external validation and interpretable models	Promising but clinically unvalidated

This supports the potential value of combined microbiota-metabolite profiling for IBS subtyping, while also showing that such tools are not yet sufficient as singular diagnostic biomarkers. Additionally, In the future, validated biomarker panels may help stratify IBS patients according to likely treatment response, but they are not currently suitable for early detection or stand-alone diagnosis (Cuevas-Sierra et al., 2019; Kase et al., 2024). Overall, recent approaches in microbiome research have produced several candidate biomarker approaches with different levels of translational readiness as summarized in Table 2.

Predicting Therapeutic Response and Patient Stratification

Currently, the research focuses on microbiome responses to low FODMAP diets. Responders show distinct baseline microbial profiles, indicating that diet alters microbial fermentation and gas production. Low FODMAP interventions improve symptoms in a substantial subset of IBS patients, but response is variable, and baseline microbiome predictors require further validation. Probiotic efficacy against FGIDs, particularly IBS, was highlighted to show response variability, as efficacy was highly strain-specific and inconsistent outcomes across trials were common (Wu et al., 2024; Éliás et al., 2023). Furthermore, microbiome-based patient stratification could eventually help distinguish likely responders from non-responders, allowing the selection of targeted therapies. Additionally, antibiotic and microbiome-targeted interventions provide short-term symptom relief but show poor long-term consistency. However, a key limitation towards stratification remains a lack of validated predictive models across populations (Mars et al., 2020; Zarei et al., 2023). This would require baseline microbiome profiling before intervention, along with integration with clinical and dietary data.

Integration Into Precision Medicine and Microbiome-Based Therapies

Precision medicine offers emerging avenues in nutrigenomics and personalised treatments based on microbiomes. Therapies can be delivered through supplementation with probiotics and prebiotics, which have been shown to support gut microbiota health and diversity. Additionally, fecal microbiota transplantation (FMT) has shown mixed results in IBS, with some trials reporting symptom improvement and

others showing limited or inconsistent benefits. Therefore, FMT should be discussed as an experimental microbiome-targeted intervention rather than an established IBS therapy. (Porcari et al., 2023; Wang et al., 2019). And while positive outcomes have been noted, mixed clinical outcomes remain the main trend, creating a limitation to application (Wahlström et al., 2016; Wang et al., 2023).

METHODOLOGICAL AND TRANSLATIONAL LIMITATIONS

Variability in Microbiome Sampling and Sequencing Methods

A major limitation in IBS microbiome biomarker research is methodological heterogeneity across studies. Stool and mucosal biopsy samples are not interchangeable because they demonstrate varying microbial populations: stool samples reflect luminal communities, whereas mucosal biopsies may better reflect host microbe interactions at the epithelial surface. Sampling time, bowel habit subtype, recent diet, antibiotic or probiotic use, bowel preparation, storage temperature, freeze thaw cycles, and DNA extraction method can all influence the microbial profiles to be detected. DNA extraction is particularly important as Gram-positive organisms may be underrepresented if cell lysis is partial. Sequencing choices also introduce variability. 16S rRNA sequencing is impacted by primer selection, amplified variable region, sequencing depth, and taxonomic reference database, while shotgun metagenomics provides higher-resolution taxonomic and functional potential but requires more complex bioinformatic processing. Therefore, differences between studies may reflect technical and analytical choices rather than validated IBS biology. Future studies should adhere to standardised collection, storage, extraction, sequencing, and bioinformatic protocols to improve reproducibility and reduce major limitation in IBS microbiome biomarker research (Shi et al., 2022; Wensel et al., 2022; Garcia Mendez et al., 2024).

Population-Specific and Environmental Influences

IBS microbiome findings are also strongly affected by population-level and environmental factors. Diet is one of the strongest modulators of gut microbiota composition and metabolite production, particularly SCFA generation from fermentable fibre. Geographic region, habitual diet, cultural dietary patterns, medication use, antibiotics, probiotics, stress, sleep,

physical activity, age, and comorbid conditions may all alter microbiome composition independently of IBS (Zhernakova et al., 2017; Malesza et al., 2021). Sex should also be treated as a biological and clinical confounder because IBS prevalence, pain sensitivity, bowel habit subtype distribution, hormonal cycling, immune responses, and microbiome composition may differ by sex (Pecyna et al., 2023). These factors reduce the universality of microbiota signatures across cohorts and may explain why IBS-associated microbial patterns vary greatly. Future biomarker studies should look to collect detailed dietary, medication, lifestyle, demographic, and clinical data and should either adjust for these variables or perform stratified analyses where appropriate.

Challenges in Reproducibility and Biomarker Validation

Reproducibility remains one of the central barriers to clinical translation. Many IBS microbiome studies are cross-sectional, which limits causal inference and makes it difficult to determine whether dysbiosis contributes to IBS pathophysiology or reflects altered diet, transit time, medication use, or symptom linked behavioural changes. Small sample sizes, inconsistent Rome criteria, variable IBS subtype classification, and differences in control selection further reduce comparability across studies. Another important limitation is the nature of composition of relative-abundance data; an apparent increase in one taxon may reflect a decrease in another rather than a true increase in absolute microbial load. Absolute quantification methods, such as qPCR, spike-in standards, or flow cytometry-informed approaches, may help address this limitation (Shen et al., 2025; Vich Vila et al., 2018). External validation is also essential because biomarker performance often decreases when tested in independent cohorts. For microbiota associated biomarkers to become clinically applicable, future studies must move beyond discovery cohorts and demonstrate reproducibility, longitudinal stability, external validity, and added clinical value over symptom-based Rome criteria.

FUTURE DIRECTIONS TOWARD VALIDATED ADJUNCTIVE BIOMARKER FRAMEWORKS

Standardisation of Microbiome Research Methodologies

Standardisation is necessary to ensure the universality of microbiota-based biomarkers and to enable

adequate microbial signature tracking across populations. Therefore, it is imperative to ensure the endorsement of standardisation for sampling protocols, storage conditions, sequencing methods, and bioinformatics pipelines. This would allow the development of consensus on reporting guidelines incorporating absolute quantification methods. To ensure controlled methodologies, the literature should reduce batch effects and technical variability as much as possible (Tegegne & Savidge, 2025).

Longitudinal Cohort Studies

Longitudinal studies are necessary for reliable indicators and are needed for causality and microbiome tracking over time. Such tracking would enable the registration of conditions before disease onset, enabling more adequate management during progression. This would also benefit from post-treatment recovery strategies. Through this, causal relationships may be established. To ensure this, large sample sizes (ideally $n > 500$) must be used, as well as a multi-centre design to improve generalisability. If this is integrated with dietary data and clinical outcomes, promising avenues can be opened within the field of microbial biomarkers (Pasolli et al., 2019; Garcia Mendez et al., 2024).

Development of Integrated Microbiome-Based Diagnostic Platforms

Multi-marker panels are a promising research direction for future adjunctive clinical stratification, combining taxonomic, metabolomic, and immune data that can be integrated into computational frameworks that may eventually support microbiome pattern analysis if externally validated. Predictive performance should be assessed using external validation, calibration, interpretability, and prospective clinical utility rather than AUC alone. The key requirements of these platforms include interpretability for clinical use. Potential outputs could be risk scores and treatment response predictions. This can be further integrated with microbiome and patient data, allowing for the development of accurate future adjunctive decision support frameworks. The future goal in this field remains to develop evidence-guided IBS stratification systems that complement symptom-based diagnosis with biological stratification (Zhang et al., 2022; Zheng et al., 2025).

CONCLUSION

IBS is increasingly understood as a heterogeneous disorder of gut–brain interaction involving altered motility, visceral sensitivity, immune activation, epithelial barrier function, and host–microbiota interactions. Current evidence supports biological plausibility for microbiota-associated biomarkers, but no reproducible microbiota-based signature has been validated for routine IBS diagnosis. Taxonomic profiles and diversity measures remain inconsistent and are strongly influenced by cohort characteristics, diet, geography, sampling methods, sequencing platforms, and analytical pipelines. Functional and metabolomic markers, including SCFAs, bile-acid profiles, and tryptophan-related metabolites, may provide more mechanistic insight than taxonomy alone, but they remain insufficiently validated as stand-alone clinical biomarkers. Immune-associated markers may add host-response information, although they are not specific to microbiota-driven IBS and overlap with other inflammatory, dietary, stress-related, and gastrointestinal conditions. Multi-omics and machine-learning approaches offer promising research frameworks for patient stratification and treatment-response prediction, but their clinical use will require standardised methods, longitudinal cohorts, external validation, interpretability, and prospective testing. Therefore, microbiota-based biomarkers should currently be viewed as investigational adjuncts to Rome-based diagnosis rather than replacements for symptom-based clinical assessment.

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A.A. contributed to conceptualisation, literature search, evidence synthesis, original draft preparation, figure preparation, and manuscript revision. A.N. contributed to supervision, validation of intellectual content, critical review, and manuscript editing. Both authors reviewed and approved the final submitted version.

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Conflict of Interest

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Ethics Statement

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