

## ROLE OF METABOLOMICS IN UNCOVERING THE MECHANISTIC LINK BETWEEN MICROBIOME MODULATION AND HOST METABOLISM

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### Review



### ABSTRACT

The gut microbiome plays a crucial role in maintaining host metabolism, immune function, and overall health. Dysbiosis, or microbial imbalance, has been linked to various metabolic, inflammatory, and neurological disorders. Microbiome-targeted therapies, including prebiotics, probiotics, postbiotics and fecal microbiota transplantation (FMT), aim to restore microbial homeostasis, but their clinical efficacy is often inconsistent due to inter-individual variability. Metabolomics, the large-scale study of small-molecule metabolites, has emerged as a powerful tool for understanding microbiome-host interactions by providing real-time insights into microbial metabolic activity. Unlike metagenomics, which focuses on microbial composition, metabolomics characterizes functional microbial outputs such as short-chain fatty acids (SCFAs), bile acids, and neurotransmitter precursors, which directly influence host physiology. This review explores the integration of metabolomics with microbiome-based interventions, highlighting its potential in elucidating treatment mechanisms, identifying predictive biomarkers, and enhancing precision medicine. We also discuss recent technological advancements, including multi-omics integration, artificial intelligence (AI)-driven data analysis, and microbiome-derived pharmaceutical developments, which are shaping the future of gut-modulation therapies. Despite its promise in personalized microbiome-based approaches, metabolomics faces challenges in standardization, regulatory approval, and clinical translation. Addressing these barriers will be essential for unlocking the full potential of metabolomics-driven gut health optimization and advancing microbiome-based precision medicine.

**Keywords:** Metabolomics, Metagenomics, Microbiome-targeted therapies, Host metabolism, Prebiotic, Postbiotic, Probiotic, FMT, Precision medicine

### INTRODUCTION

The human gastrointestinal microbiome is one of the most complex, dynamic ecological systems containing trillions of microbes, including bacteria, archaea, fungi, and viruses. These microbes are essential to the maintenance of host homeostasis by regulating metabolic functions, immune responses, and gut barrier integrity (Kho & Lal, 2018). The gut microbiota is involved in important physiological processes like nutrient metabolism, short chain fatty acid (SCFA) production, bile acid transformation, neurotransmitter synthesis, and immune modulation, all of which play a role in shaping overall health (Fan & Pedersen, 2021).

Dysbiosis, an imbalance of the gut microbiota composition and functions, has been associated with a wide range of diseases including metabolic disorders (obesity, diabetes), inflammatory bowel diseases (IBD) (Crohn's disease, ulcerative colitis), neurodegenerative diseases (Parkinson's, Alzheimer's) and even cancers (O'Toole *et al.*, 2017). The pathways by which gut microbes impact these diseases are complex and frequently require gut barrier dysfunction, chronic inflammation, immune dysregulation, or changes to microbial byproducts (Lynch & Pedersen, 2016). This increasing understanding of the gut microbiome's contribution to health and disease has created interest in microbiome-based interventions such as prebiotics, probiotics, postbiotics, and fecal microbiota transplantation (FMT), with the goal of restoring microbial homeostasis and enhancing host physiology (Gibson *et al.*, 2017).

These microbiome-targeted therapies are exciting, but their transition into clinical use is not straightforward because of significant inter individual variation in the composition of the gut microbiome, which in turn affects how an individual responds to prebiotics, probiotics, or other strategies (Zhao, 2013). Furthermore, we still lack a full understanding of how microbiome modulation impacts host metabolism, immune function, and disease progression (Nicholson *et al.*, 2012). Conventional microbiome research has concentrated on sequencing metagenomes, providing relative insight into microbial composition while incapable of revealing functional metabolic activity in real time (Dorrestein *et al.*, 2014). This limitation is significant because microbial metabolism is highly dynamic and context-dependent, and real-time functional insights are essential to understanding how microbiota respond to environmental or therapeutic changes (Wishart, 2019). As

a result, functional readouts of microbial metabolism are required to establish how gut microbes affect host physiology and therapeutic responses.

Metabolomics has become an established technology for analyzing real-time metabolite alterations resulting from microbial activity and therapeutic measures. Metabolomics is the large-scale study of small-molecule metabolites found in biological systems and offers a snapshot of host metabolic status and microbiome-derived metabolites (Han *et al.*, 2021). While metagenomics detects microbial DNA sequences, metabolomics reflects a functional snapshot of microbial activity by monitoring, detecting, and quantifying bioactive microbial metabolites like SCFAs, bile acids, polyphenols, and neurotransmitter precursors (Martinez *et al.*, 2017). These metabolites serve as important bridges between microbiome and host, influencing metabolic, immune, and even neurological pathways (Hertli & Zimmermann, 2022).

The combination of metabolomics with microbiome based therapeutics has relevant implications in clinical contexts. Metabolomics can help identify biomarkers relevant to disease states and treatment responses, enabling the partitioning of patients into responders and non-responders and thus increasing the opportunity to personalized therapies (Peters *et al.*, 2018). In addition, metabolomics can help to identify novel metabolic pathways that contribute to host health, which can facilitate development of next-generation microbiome-targeted interventions, such as engineered probiotics and microbiome-derived pharmaceuticals (Riglar & Silver, 2018).

### Scope of This Review

This review explores the integration of metabolomics in microbiome-based therapeutics, focusing on its role in:

1. Elucidating mechanisms of microbiome-targeted therapies, including prebiotics, probiotics, postbiotics, and FMT.
2. Identifying microbial metabolites that serve as biomarkers for disease progression and treatment responses.
3. Enhancing precision medicine through artificial intelligence (AI)-driven metabolomic analysis and multi-omics integration.
4. Addressing technological and regulatory challenges in translating microbiome-metabolomics research into clinical applications.

By bridging the gap between microbiome modulation and host metabolism, this review highlights the transformative potential of metabolomics in optimizing gut-targeted therapies and advancing precision medicine.

## MICROBIOME – BASED THERAPEUTICS

Microbiome-based therapeutics have emerged as a promising approach to modulating gut health and treating a range of diseases. Among the most commonly investigated interventions are prebiotics, probiotics, postbiotics and FMT, which all affect the gut microbiome via different mechanisms. Unlike probiotics, prebiotics are generally considered indigestible substrates that serve as fuel for gut-adjacent microorganisms that are most beneficial to the host, particularly members of the *Bifidobacterium* and *Lactobacillus* genera (Gibson *et al.*, 2017). Compounds are also known to promote SCFA production including inulin, fructooligosaccharides (FOS), galactooligosaccharides (GOS), and resistant starch which increase butyrate, acetate, and propionate production. SCFAs have an important role in gut homeostasis as they can enhance intestinal barrier function, regulate immune response, and in addition they serve as an energy source for colonocytes (Makki *et al.*, 2018). Prebiotics have been extensively researched, mainly focused on alleviating gastrointestinal conditions like irritable bowel syndrome (IBS) and IBD, along with metabolic disorders that include obesity and type 2 diabetes (Canfora *et al.*, 2019). Certainly, prebiotics have been reported to influence the gut-brain axis, as emerging evidence suggest that prebiotics promote serotonin synthesis and may help to reduce symptoms of anxiety and depression (Silva *et al.*, 2020). Nevertheless, prebiotic interventions encounter issue of inter-individual differences in gut microbial composition, impacting their metabolic fate and efficacy (Zhao *et al.*, 2018). Furthermore, there is a restriction in wider use of fermentable fibers due to the potential for gastrointestinal discomfort, such as bloating and gas, following their excessive intake (Canfora *et al.*, 2019). While prebiotics target existing helpful microbes, another significant therapeutic strategy is the direct introduction of live beneficial microorganisms, known as probiotics." Probiotics, which are defined as live microorganisms that, when administered in adequate amounts, confer a health effect on the host, have been widely investigated for modulation of gut health (Hill *et al.*, 2014). *Lactobacillus* and *Bifidobacterium* represent the most commonly studied probiotic strains, but other species, such as *Saccharomyces* and *Escherichia coli* Nissle, have also shown clinical relevance (Fijan, 2014). Probiotics act by diverse means, from direct microbial competition with pathogens reducing their colonization, to altering immune responses through regulation of local and systemic levels of cytokines, and generating bioactive metabolites manipulating host physiology (O'Toole *et al.*, 2017). Probiotics are clinically effective in reducing the onset and severity of antibiotic-associated Diarrhoea, notably in the case of *Clostridioides difficile* infection (CDI) (Lau & Chamberlain, 2016). Additionally, they have been investigated for their potential in managing IBD, IBS, obesity, and metabolic syndrome (Klemashevich *et al.*, 2014). Some probiotic strains, such as *Lactobacillus gasseri*, have been associated with reductions in visceral fat and body weight, suggesting their role in obesity management (Canfora *et al.*, 2019). However, probiotic interventions are limited by strain-specific effects, survivability issues during gastrointestinal transit, and the transient nature of colonization, which necessitates continuous supplementation to maintain benefits (Zhao *et al.*, 2018). The heterogeneity of clinical responses further complicates their therapeutic application, as individual microbiome variations influence probiotic engraftment and function (Brüssow, 2019). Given the challenges associated with live probiotic organisms, such as viability and colonization, researchers have focused on the medicinal potential of the bioactive substances produced by these microorganisms, known collectively as postbiotics.

Postbiotics are bioactive microbial byproducts that provide health benefits without the need for live microorganisms. Unlike probiotics, which require bacterial survival and colonization in the gut, postbiotics directly deliver functional metabolites such as SCFAs, exopolysaccharides, organic acids, peptides, and bacteriocins, all of which contribute to immune modulation, gut barrier integrity, and anti-inflammatory effects (Aguilar-Toalá *et al.*, 2018). Of these, butyrate has been most studied for its capacity to promote intestinal barrier function as it is an energy source for colonocytes and can upregulate tight junction proteins (Peng *et al.*, 2007). An exopolysaccharide also serves as a prebiotic-like molecule that can selectively stimulate beneficial gut microbes (Aguilar-Toalá *et al.*, 2018). Similarly, bacteriocins and bacterial peptides promote gut homeostasis by preventing pathogen colonization (Shenderov, 2013). One of the primary benefits of postbiotics is that they do not depend on the live viability of a bacterium for efficacy, and are therefore simpler to formulate into pharmaceutical or nutraceutical products. In addition, postbiotics were shown to have homogeneous effects and are independent of the baseline microbiota composition—thereby decreasing variability of therapeutic outcomes (Shenderov, 2013). These features render postbiotics a better choice compared to traditional probiotics, especially in cases of gut microbiome impairment caused by antibiotic treatment or chronic gastrointestinal disorders. Despite their potential, postbiotics face several limitations. The absence of standardisation is one of the key challenges, as the clinical application of these therapies is not supported by clear dosage guidelines or regulatory frameworks. Current debates also center around the definition of postbiotics, with some researchers arguing for the inclusion of inactivated

microbial cells or cell fragments, while others define postbiotics strictly as purified microbial metabolites devoid of cellular components (Aguilar-Toalá *et al.*, 2018). This lack of consensus complicates both clinical translation and product development. Additionally, there is an ongoing scientific debate between using complex postbiotic mixtures (which may better mimic natural microbial effects) versus purified, well-defined compounds (which are easier to standardize and study mechanistically) (Salminen *et al.*, 2021). While complex mixtures might offer synergistic benefits, their compositional variability raises concerns about reproducibility, safety, and regulatory classification. Moreover, although postbiotics have exhibited positive effects, mechanistic pathways and interactions between postbiotics and their host have not been comprehensively elucidated, leading to an adverse impact on the widespread use of postbiotics in precision medicine (Liu *et al.*, 2023). Another limitation is that, unlike probiotics, postbiotics may not confer strain-specific benefits that are specific to the profile of individual gut microbiomes (Ji *et al.*, 2023). The advancement of postbiotics-based therapies lies in metabolomics-driven research for the identification of new bioactive compounds, as well as their therapeutic potential and combination with precision nutrition strategies (Liu *et al.*, 2023). Beyond specific microbial products, a more comprehensive strategy to restore a dysbiotic microbiome is transferring an entire microbial community through FMT.

FMT, a promising microbiome-targeted approach, has shown tremendous clinical efficacy in the management of recurrent CDI. FMT is the transplant of fecal bacteria from a healthy donor into a recipient to restore microbial diversity and functional stability. Studies have reported cure rates higher than 85% in CDI patients receiving FMT, even better than antibiotic treatment (Cammarota *et al.*, 2017). Though clinical data supporting FMT remain complex, its therapeutic success results from repopulating the gut microbiota with a diverse microbial community capable of increasing SCFA production, bile acid metabolism, and immunomodulatory pathways (Baktash *et al.*, 2018). In addition to CDI, FMT also has been investigated as a therapeutic modality in IBD, metabolic disorders, and even neurodegenerative disease (O'Toole *et al.*, 2017). Yet, outcomes in these conditions are heterogenous, reflecting that FMT efficacy is shaped by the microbiome composition of the donor, the resilience of the recipient microbiome, and the pathology of the original disease (Segal *et al.*, 2020). And although there are some patients that have profound clinical changes after FMT, others have short-term or no effect, pointing to the need for further exploration of the mechanisms of microbial engraftment and functional restoration. Key challenges for the broad use of FMT also lie in safety issues such as the risk of transmission of opportunistic pathogens and the long-term effects of gut microbiome modification (Cammarota *et al.*, 2017). Regulatory frameworks around FMT implementation are also patchy, with current use as an approved treatment limited largely to CDI (O'Toole *et al.*, 2017). To improve the safety and reproducibility of the outcomes of FMT, it is important to standardize donor screening, stool processing, and delivery methods (Nigam *et al.*, 2022).

To overcome the limitations associated with traditional microbiome-based therapies, next-generation microbiome therapeutics are being developed using advances in synthetic biology and microbial engineering. Engineered probiotics conjugate a new class of therapeutics that are capable of promulgating specialized functions not found in typical, natural-origin probiotics. Example: *Escherichia coli* Nissle has been genetically engineered to secrete butyrate, an important SCFA with anti-inflammatory properties, for IBD therapy (Charbonneau *et al.*, 2020). Engineering of various *Lactobacillus* strains for secretion of immunomodulatory cytokines to regulate gut inflammation has been similarly pursued (Riglar & Silver, 2018). One advantage of these engineered probiotics is their specificity because they can be designed to inhibit specific metabolic pathways or microbial populations associated with diseases (Charbonneau *et al.*, 2020). Moreover, synthetic microbiome consortia consisting of several engineered microbial species are being explored as an approach to reproduce the functional complexity of a healthy gut microbiota. To achieve this goal, stable colonization, predictable metabolic outputs are necessary, which synthetic consortia could offer to solve the variability of natural probiotic therapies (Riglar & Silver, 2018).

Microbiome-derived small molecule therapeutics is another potential approach to precision medicine. Rather than the introduction of live bacteria, researchers are defining and utilizing bioactive metabolites generated by gut microbes with beneficial impacts on the health of the host. For instance, secondary bile acids that are metabolized by gut microbiota have been associated with modulation of metabolic and inflammatory pathways (Brown & Hazen, 2017). Likewise, it has been shown that microbial metabolites produced from polyphenols, such as urolithins, may also work in improving mitochondrial functioning and decreasing age-related inflammation (Vini *et al.*, 2022). By isolating and providing these metabolites as pharmaceutical compounds, microbiome-based therapies can also effect site-specific biological changes without concern about managing live microbes (Charbonneau *et al.*, 2020).

In conclusion, prebiotics, probiotics, and FMT have demonstrated clinical benefits, their widespread application is limited by variability in patient responses, strain-specific effects, and regulatory challenges. Next-generation approaches, including engineered probiotics, synthetic microbial consortia, and microbiome-derived small molecules, offer more targeted and mechanistically precise alternatives. However, further research is needed to refine these strategies, ensure safety, and develop standardized protocols for clinical implementation. The future of

microbiome-based therapeutics lies in the integration of systems biology approaches that provide deeper insights into microbial functions, host interactions, and therapeutic outcomes.

**Table 1** Comparative Overview of Gut Modulation Therapies: Mechanisms, Metabolites, Applications, and Challenges

Therapeutic Approach	Mechanism of Action	Key Metabolites	Clinical Applications	Challenges & Limitations
Prebiotics	Stimulate beneficial gut microbes, increase SCFA production	SCFAs, lactate	IBS, metabolic disorders, gut health (Canfora et al., 2019)	Individual response variability, gastrointestinal discomfort (Zhao et al., 2018)
Probiotics	Introduce beneficial microbes that modulate gut microbiota and immune response	SCFAs, antimicrobial peptides, neurotransmitters such as gamma-aminobutyric acid (GABA) and serotonin	Antibiotic-associated diarrhea, IBD, obesity, neuropsychiatric conditions (Hill et al., 2014)	Strain-specific effects, survivability issues, transient colonization (Zhao et al., 2018)
Postbiotics	Bioactive microbial metabolites exert physiological effects without live bacteria	SCFAs, exopolysaccharides, organic acids, peptides	Inflammation reduction, gut barrier improvement, metabolic regulation (Aguilar-Toalá et al., 2018)	Lack of standardization, unclear dosing guidelines (Shenderov, 2013)
Fecal Transplantation (FMT)	Restores microbial diversity and functional stability	SCFAs, bile acids, tryptophan derivatives	CDI, IBD, metabolic disorders (Cammarota et al., 2017)	Donor selection, safety concerns, regulatory challenges (Nigam et al., 2022)

**THE POWER OF METABOLOMICS TO ENHANCE MICROBIOME-BASED THERAPIES**

The emergence of metabolomics, a comprehensive discipline for the analysis of small-molecule metabolites produced in biological systems, as an approach in microbiome studies has transformed the field by allowing for functional characterization of microbes through the in vivo examination of microbial activity in real time. While metagenomics reveals microbial DNA sequences with details at the taxonomic level, metabolomics reveals a dynamic snapshot of microbial function via bioactive metabolites, which include SCFAs, bile acids, polyphenols, and neurotransmitter precursors (Wishart, 2019). These metabolites are crucial in interactions between microbiome and host metabolic pathways, immune system, neurological processes (Dodd et al., 2017). With the variability and diversity seen in microbiome-targeted therapies, metabolomics provides a much-needed functional dimension of investigation to better stratify their targets and increase efficacy (Zhang et al., 2019). Prebiotics, probiotics, postbiotics, and FMT are examples of microbiome-based interventions that have the potential to restore gut microbial balance and improve host health. However, these interventions are often limited by variable treatment responses and a lack of mechanistic understanding, challenges that metabolomics can effectively address (Cohen et al., 2017). A huge problem with interventions at the microbiome level, however, is the imperfect understanding of how they function. Metabolomics can help fill this gap by characterizing the metabolic outputs of gut microbes and also their interactions with host physiology. One example would be prebiotic compounds, including inulin, GOS, and resistant starch, which preferentially foster growth of the beneficial gut bacteria, primarily *Bifidobacterium* and *Lactobacillus*, leading to the production of SCFAs like butyrate, acetate, and propionate (Canfora et al., 2019). However, interindividual differences in gut microbiota composition greatly influence prebiotic metabolism, which in turn influences SCFA production and clinical efficacy of the treatment (Salonen & de Vos, 2014). Metabolomic profiling has demonstrated that individuals with a higher baseline abundance of butyrate-producing bacteria respond more favorably to prebiotic interventions, supporting the use of metabolic biomarkers for patient stratification (Marinos et al., 2023). Likewise, probiotics influence their activity through various mechanisms including competitive inhibition of pathogens, immune modulation, and the generation of bioactive compounds. Probiotic efficacy is however very strain specific and dependent on the host microbiome composition (Ouweland, 2017). In particular, metabolomics has been essential to highlight the major metabolites secreted by probiotics, such as lactic acid, antimicrobial peptides, and indole derivatives, which play beneficial roles in gut homeostasis and immune modulation (Poyet et al., 2019). Additionally, metabolomic analyses have shown that individuals who respond to probiotics have different baseline metabolic signatures than non-probiotic responders, and higher baseline levels of bile acids and tryptophan metabolites can predict better treatment outcomes (Suez et al., 2019). Metabolomics could allow tailoring probiotic treatment to the metabolic fingerprint of an individual. Postbiotics are bioactive microbial byproducts, being SCFAs, exopolysaccharides, peptides or bacteriocins, complementing live probiotic therapies through direct administration of beneficial metabolites (Aguilar-Toalá et al., 2018). The field of metabolomics has been instrumental in uncovering the mediating pathways by which

postbiotics elicit their observed effects such as the ability of butyrate and propionate to enhance intestinal barrier function and modulate inflammation (Pelton, 2020). By comparison with the probiotics, postbiotics deliver uniform therapeutic outcomes regardless of the composition of an individual's microbiome, thus minimizing variability of response (Markowiak-Kopeć & Śliżewska, 2020). The absence of standardized dosing guidelines and regulatory frameworks, however, presents a formidable challenge, highlighting the importance of embedding metabolomics in clinical validation (Kumar et al., 2024). FMT has emerged as one of the most successful microbiome-based interventions, particularly in treating recurrent CDI, where cure rates exceed 85% (van Nood et al., 2013). Beyond CDI, FMT is being explored as a therapeutic option for IBD, metabolic disorders, and even neurodegenerative diseases (O'Toole et al., 2017). However, its efficacy in these conditions remains inconsistent due to variations in donor microbiota composition, recipient gut resilience, and underlying disease pathology (DeFilipp et al., 2019). Metabolomics has played a critical role in elucidating the metabolic changes associated with successful FMT, revealing that responders exhibit rapid restoration of secondary bile acid production, while non-responders show persistent dysbiosis-related metabolic imbalances (Seekatz et al., 2018). These findings emphasize the potential of metabolomics in optimizing donor selection and improving FMT outcomes through metabolite-based patient profiling. The other important application of metabolomics in microbiome-based therapies is its potential to predict responses to treatment and to tailor interventions to individual metabolic profiles. For example, the identification of biomarkers that distinguish responders from non-responders can be accomplished by assessing pre- and post-intervention metabolite levels (Dorrestein et al., 2014). For instance, individuals with higher baseline SCFA precursor levels tend to benefit more from prebiotic supplementation, while probiotic efficacy has been linked to initial bile acid composition and microbial tryptophan metabolism (Sanna et al., 2019). Likewise, FMT success rates have been associated with pre-treatment microbial diversity and bile acid profiles, so the incorporation of metabolomics into precision medicine strategies is advocated (Smillie et al., 2018). In addition, real-time, dynamic metabolic monitoring provides the ability to evaluate the effectiveness of the applied therapy in an ongoing fashion and adapt the interventions to the changing metabolic status of the subject (Clemente-Suárez et al., 2023). In addition to fine-tuning existing microbiome-based therapies, metabolomics has enabled the identification of new bioactive compounds derived from microbes that hold therapeutic promise. Instead of relying on live microbial interventions, researchers are now isolating and administering beneficial metabolites directly as pharmaceuticals. For example, urolithins, microbial metabolites derived from polyphenols, have demonstrated anti-inflammatory and mitochondrial-enhancing properties, suggesting their potential use in aging-related conditions (Vini et al., 2022). Likewise, secondary bile acids and microbial neurotransmitters such as precursors of GABA and serotonin have also proven beneficial in modulating metabolic and mental health disorder (Pokusaeva et al., 2017). Emerging synthetic biology techniques have also allowed for the engineering of next-generation probiotics with improved functional capabilities. One such strain, *Escherichia coli* Nissle, has been genetically modified to generate butyrate for treating IBD (Charbonneau et al., 2020), whilst *Lactobacillus* which have been engineered to secrete anti-inflammatory cytokines provides targeted immune modulation. Additionally, synthetic microbiome consortia could be engineered to recapitulate

the functional diversity present in a healthy gut microbiota, ensuring stable colonization and predictable metabolic contributions (Oliphant & Allen-Vercoe, 2019).

In conclusion, metabolomics has revolutionized microbiome research by providing real-time insights into microbial metabolism and its impact on host health. By elucidating mechanisms of action, predicting treatment responses, and identifying novel therapeutic targets, metabolomics enhances the precision and efficacy of microbiome-based therapies. As the field advances, integrating metabolomics with multi-omics approaches—including metagenomics, transcriptomics, and proteomics—will enable a deeper understanding of host-microbiome interactions. This systems biology approach holds the potential to unlock new frontiers in personalized medicine, paving the way for next-generation microbiome-based therapeutics.

## TECHNOLOGICAL ADVANCES IN MICROBIOME-METABOLOMICS RESEARCH

Novel analytical and computational technologies have propelled the field of microbiome-metabolomics research to new heights. These developments enabled researchers to start thinking not only about the identification of microbial species, but also their functional roles in the health and disease of their host. Key technologies in this domain include mass spectrometry (MS) and nuclear magnetic resonance (NMR) spectroscopy for metabolite detection, multi-omics integration for comprehensive biological insights, and AI/machine learning (ML) for data analysis and predictive modeling, with MS and NMR often used complementarily to achieve comprehensive metabolite detection. These methods offer enhanced understanding of microbiome-host dynamics, leading to identification of potential targets for novel therapeutic intervention and personalized treatment options (Schrimpe-Rutledge *et al.*, 2016).

### MS in Metabolomics

MS is one of the most common methods applied in metabolomics due to its high sensitivity, specificity and wide dynamic range. MS works by ionising metabolites, determining their mass-to-charge ratios and detecting them accurately. It has the potential to be combined with separation methods like gas chromatography (GC-MS) or liquid chromatography (LC-MS) to obtain higher-resolution metabolomes (Zhang *et al.*, 2020). The biggest strengths of MS are the detection of thousands of metabolites, even at low concentrations, making it perfectly suited to studying microbial metabolism in complex biological samples like stool, urine, and plasma (Dunn *et al.*, 2011).

With respect to microbiome research, MS has allowed to discern key microbial metabolites such as SCFAs, bile acids, polyphenols, and neurotransmitter precursors, all of which play critical roles in host metabolism and immune function (Bauermeister *et al.*, 2022). MS-based metabolomics has been applied to study conditions such as IBD, metabolic syndrome, and neurodegenerative diseases, where microbial metabolites significantly impact disease progression (Visconti *et al.*, 2019). Limitations of MS include the extensive sample preparation required, which can introduce variability. Moreover, ion suppression effects can also lead to biased metabolite quantification in MS, high instrument costs and the need for specialists limit accessibility (Sindelar & Patti, 2020). Recent advances in high-resolution MS (HR-MS) have improved metabolite identification accuracy, while ion mobility spectrometry-MS (IMS-MS) has generated better metabolite separation, which helped to alleviate ion suppression effects (Patti *et al.*, 2012) despite these challenges. In addition, the use of direct-infusion MS (DI-MS) has simplified sample processing as it has helped to overcome sample-preparation hurdles leading to reduced preparation times and increased throughput (Patti *et al.*, 2012).

### NMR Spectroscopy in Metabolomics

NMR spectroscopy is another powerful tool for metabolomic analysis, having the advantage of high reproducibility and being relatively non-destructive. NMR operates by subjecting the metabolites to a strong magnetic field where their energy can be absorbed and re-emitted; this provides in-depth structural information (Emwas *et al.*, 2013). In contrast to MS, which is expensive and often requires ionization, high temperature, and prolonged sample processing, in NMR no thermal treatment is needed, allowing for in vivo direct analysis of biological fluids, making it a candidate for longitudinal microbiome studies (Wishart, 2019).

To profile microbial metabolites, NMR has been applied extensively to fecal, urine and blood samples, revealing gut microbial activity and its influence on host metabolism (Louis & Flint, 2017). A notable application of NMR-based metabolomics has been to study alterations in microbial metabolism under different contexts such as dietary interventions and in response to probiotic supplementation and FMT (Beckonert *et al.*, 2007). Whilst NMR is known for its good reproducibility and quantitative accuracy, it has lower sensitivity compared to MS and is generally less applicable for the detection of low-abundance metabolites. NMR requires a larger sample volume, which is an issue clinically. However, advancements such as cryogenically cooled probes have significantly improved sensitivity, while hyperpolarization techniques, such as dynamic nuclear polarization-NMR (DNP-

NMR), have increased signal strength, expanding the applicability of NMR in microbiome research (Letertre *et al.*, 2021).

It is vital to highlight that MS and NMR are often viewed as complimentary rather than competitive technologies. The high sensitivity and broad metabolite coverage of MS, combined with the high reproducibility, quantitative accuracy, and structural information provided by NMR, mean that combining the two techniques can provide a more comprehensive and robust characterization of the metabolome than either method alone.

Besides instrumental progress, metabolomics strongly depends on advanced data analysis strategies to decrypt intricate datasets. Techniques such as principal component analysis (PCA) and orthogonal partial least squares discriminant analysis (OPLS-DA) provided by multivariate statistical methods are useful for extracting the most important metabolomic patterns while reducing dimensionality (Worley & Powers, 2013). Pathway analysis, including metabolite set enrichment analysis (MSEA) and Kyoto Encyclopedia of Genes and Genomes (KEGG) mapping, provides insights into metabolic alterations associated with disease states. Network-based analyses such as reconstruction of the metabolic network leverage multi-omics datasets to infer host-microbiome interactions. These computational approaches magnify the strength of metabolomics as they can disclose novel metabolic pathways and putative clinical targets (Hasin *et al.*, 2017).

### Multi-Omics Integration in Microbiome Research

Combining metabolomics with other omics technologies, including genomics, transcriptomics, and proteomics, has transformed microbiome research by offering a comprehensive perspective of microbial functions and host interactions. Genomics offers information on the taxonomic composition of the microbiome, transcriptomics reveals gene expression, proteomics identify functional proteins, and metabolomics evaluate biochemical outputs (Hasin *et al.*, 2017). This multi-omics approach helps bridge the gap between microbial genetic potential and actual metabolic activity, allowing for a deeper understanding of how gut microbes influence host health (McHardy *et al.*, 2013).

Multi-omics integration has an important application in personalized medicine, where integration of metabolomic data with gut microbiome sequencing can be used to best predict individual responses to dietary interventions, prebiotics, and probiotics (Zierer *et al.*, 2018). Moreover, multi-omics approaches have been employed to discover new biomarkers for various diseases including colorectal cancer and metabolic disorders, facilitating the development of targeted microbiome-focused therapies (Dar *et al.*, 2023). Yet multi-omics is a challenge because it requires standardized data processing pipelines, computational tools to work with the large datasets produced and also the correlation between different types of data poses a challenge (Gomez-Cabrero *et al.*, 2014). Recent developments in bioinformatics and systems biology have made it possible to overcome some of these challenges and support better multi-omics analyses (Misra *et al.*, 2019).

### AI and ML in Microbiome- Metabolomics Research

AI and ML have made significant contributions to microbiome- metabolomics research, where they can analyze vast and complex datasets, identifying deep hidden or dimensionality patterns in data, a task that is challenging using classical statistical approaches (Chi *et al.*, 2024). ML algorithms may be applied to large metabolomic datasets to classify microbial metabolic profiles or predict risk of disease based on metabolites derived from the microbiome (Noecker *et al.*, 2017). Computational methods are particularly helpful in microbiome-centered personalized medicine, as AI models can distinguish between responders and non-responders to specific interventions such as probiotics, prebiotics, and FMT (Heintz-Buschart & Wilmes, 2018).

Different ML algorithms are used for specific tasks in metabolomics. For biomarker discovery, supervised learning algorithms, including Random Forest (RF), Support Vector Machines (SVM), and PLS-DA are widely applied to classify metabolic profiles and to identify prominent biomarkers for differentiating healthy and diseased state (Noecker *et al.*, 2017). The Least Absolute Shrinkage and Selection Operator (LASSO) regression, which facilitates feature selection by removal of redundant or non-informative metabolites in large data sets (K. Wang *et al.*, 2022).

For disease prediction on the basis of metabolomic signatures, deep learning predictive models like neural networks, convolutional neural networks (CNNs), and recurrent neural networks (RNNs) can be employed to provide insights on personalized interventions (Zeevi *et al.*, 2015). Gradient boosting algorithms like XGBoost and LightGBM also improve prediction accuracy by accommodating complex nonlinear relationships between metabolites (Magnúsdóttir *et al.*, 2017). In microbiome-metabolome network analysis, AI-driven graph-based models are employed to study metabolite interactions with microbial communities; these interactions can lead to the discovery of key functional microbial hubs that drive disease progression (Heintz-Buschart & Wilmes, 2018). Commonly used unsupervised clustering algorithms such as K-means, hierarchical clustering, t-SNE, and UMAP are also applied to cluster the samples based on metabolomic signatures and uncover sub-phenotypes of various metabolic disorders (Gilbert *et al.*, 2016).

Standardized performance metrics are critical to validating AI models in microbiome-metabolomics studies. To evaluate the generalizability of the models, cross-validation techniques, such as K-fold cross-validation and Leave-One-Out Cross-Validation (LOOCV), were applied (Giuffrè *et al.*, 2023). Performance metrics, including accuracy, sensitivity, specificity, and area under the receiver operating characteristic (AUC-ROC) curve, quantify a model's ability to differentiate between various metabolic states. The root mean square error (RMSE) and mean absolute error (MAE) are also commonly used evaluation metrics for metabolite concentration prediction models. Also, permutation testing and external validation cohorts are critical—you want to make sure that your AI-driven biomarker discoveries are both robust and generalizable.

AI-based microbiome research has shown potential in diagnostics and therapeutics already. For example, the application of deep-learning models trained on gut microbiome and metabolomic profiles has allowed for accurate predictions of individual response patterns to dietary interventions and identification of microbial signatures associated with type 2 diabetes (Zeevi *et al.*, 2015). AI has also been employed to reconstruct microbial metabolic networks, allowing researchers to simulate microbial community interactions and responses to environmental changes (Magnúsdóttir *et al.*, 2017).

Despite these advantages, AI-based microbiome research faces challenges, one of the most prominent being the “black box” nature of many ML models—particularly deep learning—where the internal decision-making process is opaque and not easily interpretable by clinicians or researchers. This lack of transparency can hinder clinical trust and regulatory approval. To overcome this, Explainable AI (XAI) techniques are increasingly integrated to elucidate how models arrive at their conclusions, thereby supporting transparency, improving clinical decision-making, and fostering trust in AI-guided interventions (Adadi & Berrada, 2018). These methods are critical for translating AI research into clinical applications where interpretability, accountability, and safety are paramount.

Improved technology for microbiome-metabolomics research (e.g., MS, NMR, multi-omics integration, AI/ ML) has expanded our capability to interrogate microbiome-host interactions and enable the discovery of novel therapeutic approaches. MS offers ultra-sensitive detection of metabolites, whereas NMR is reproducible and provides structural details. The integration of multi-omics approaches is critical to comprehensively characterizing microbial functions, while AI-based approaches have the potential to support prediction and provide personalized interventions. Despite the obstacles present with these technologies, advancements in analytical methods, bioinformatics, and computational modeling continue to advance the field, and microbiome-based precision medicine is reaching for clinical translation.

## CLINICAL TRANSLATION AND PERSONALIZED MEDICINE

Integrating metabolomics with clinical practice has the potential to transform personalized medicine through the tailoring of therapeutic interventions based on metabolic signatures. Metabolomics enables the identification of individualized biochemical signatures reflective of an individual's microbiome composition, metabolic state, and disease status (Wishart, 2019) - unlike traditional methods that employ a standardized treatment approach. Thus, using this data, microbiome-based therapies such as prebiotics, probiotics, postbiotics, and FMT can be personalized to achieve efficacy and minimize adverse effects. However, the application of metabolomics research into clinical practice takes time due to standardization, inter-individual variability, and regulatory issues. Overcoming these challenges is essential for unlocking the promise of metabolomics to personalize medicine.

### Personalized Medicine Through Metabolomics

Metabolomics enables precision medicine by providing real-time insights into how an individual's microbiome interacts with their metabolism. Conventional microbiome studies focus on profiling microbial composition via metagenomics, an approach that fails to assess functional metabolic activity. Metabolomics adds to genomic and microbiome data by measuring bioactive microbial metabolites that directly impact host physiology, such as SCFAs, bile acids, neurotransmitter precursors, and polyphenols (Muller *et al.*, 2022). By studying these metabolic signatures, clinicians are able to predict a patient's likely response to any microbiome-based intervention, and to tailor treatment accordingly (Korpela *et al.*, 2014).

For instance, prebiotic supplementation has been reported to promote the growth of favorable bacterial populations, which in turn, augments SCFA production to support gut barrier integrity and metabolic health (Canfora *et al.*, 2019). Due to interindividual differences in gut microbiota composition, SCFA production is variable across individuals leading to non-ideal clinical outcomes (Salonen & de Vos, 2014). Metabolomic profiling can be used to identify patients at baseline with a metabolic signature more likely to respond to prebiotic therapy to facilitate targeted and effective intervention. Probiotics have also been demonstrated exerting strain-specific effects based on host-microbiome interactions. By identifying whether a probiotic strain makes metabolites that could be beneficial to a subject,

metabolomics moves away from the trial-and-error methods currently used in probiotic therapy (Zeevi *et al.*, 2015).

FMT is a very promising therapy for recurrent CDI and has been variable in effectiveness for IBD and metabolic disorders (Camarota *et al.*, 2017). One of the main reasons for this variability is the complex interaction between donor and recipient microbiomes. Likewise, metabolomics could be applied to the selection of donors, aiming to find the metabolic profile that is associated with successful outcomes of FMT (Seekatz *et al.*, 2018). For instance, recipients that have lower baseline levels of secondary bile acids — an important metabolite involved in microbial-host interactions — will respond better to donors with metabolically diverse microbiome (Godlewska *et al.*, 2022). This strategy extends to engineered probiotics and postbiotic therapies, wherein metabolomic data is leveraged to formulate curated microbial-derived metabolites to enable precision treatment (Ole, 2013).

### Challenges in Clinical Translation of Metabolomics

Although promising, there are challenges to implementing metabolomics in the clinical practice. The lack of the state of the art standardization is one of the greatest barriers to metabolomics. Diverse analytical platforms between laboratories like MS and NMR spectroscopy lead to discrepancies in metabolite identification and quantification as well (Sindelar & Patti, 2020). Reproducibility and comparability require standardized protocols across the stages of sample collection and processing and data interpretation (Dunn *et al.*, 2011). Many of these issues have been addressed by the Metabolomics Standards Initiative (MSI), which is focused on providing common practices for metabolomic research and clinical application (Sumner *et al.*, 2007).

Another challenge is inter-individual variability in metabolomes, where diet, genetics, medication use, and environmental exposures all affect metabolic profiles, resulting in unequal treatment response. Population-wide studies and the application of novel AI-assisted patient stratification to identify personalized metabolic signatures will be key to properly addressing this issue and precision medicine approaches (Zierer *et al.*, 2018) (Hasin *et al.*, 2017). Furthermore, metabolomics involves a dynamic and non-static dataset, and insufficient computational tools remain a major barrier to accurate data interpretation. Combining multi-omics strategies such as genomics, transcriptomics, and proteomics can increase the confidence in the identified biomarkers and offer insight into the systems level study of metabolic pathways, leading to targeted therapeutic avenues (Hasin *et al.*, 2017).

Translating metabolomics research into clinical applications is also challenged by regulatory considerations. Metabolomics produces complex and multidimensional data unlike any traditional diagnostic test that requires sophisticated computational data-analysis and-interpretation methods. Current regulatory bodies, such as the U.S. Food and Drug Administration (FDA), have not yet provided the framework for the clinical validation and approval of metabolomics-based diagnostics and therapeutics (Trifonova *et al.*, 2023). Moving forward with metabolomics, it will be essential to create standardized clinical protocols, and prove utility of these metabolomic biomarkers using rigorous validation studies to obtain regulatory acceptance (Long *et al.*, 2020).

The integration of metabolomics into clinical practice is already reshaping the way microbiome-based treatments are used. Probiotics and prebiotics have typically been marketed as general health supplements for people as needed, with little personalization. Metabolomics provide a more targeted way to go about it, so that only those with compatible microbiome profiles receive specific probiotic or prebiotic formulations (Suez *et al.*, 2019). Guided by improved understanding, allows more specific interventions rather than empirical supplementation. Metabolomics has already proven to be successful in this other field of clinical applications. Metabolomics-based markers have also improved the early detection of cancers, such as colorectal and breast cancer, by identifying distinct metabolic signatures between malignant and non-malignant states (Visconti *et al.*, 2019). In cancer research, Plasma metabolomics has revealed lipid and amino acid biomarkers predictive of cardiovascular risk and heart failure progression in cardiovascular disease (CVD) (Wishart, 2019). In the context of gastrointestinal disorders, fecal metabolomics has been employed to distinguish between IBD and IBS, resulting in improved accuracy in diagnosis and treatment selection (Louis & Flint, 2017). In addition, novel microbiome-derived therapeutics are being developed using metabolomics. Instead of just attempting live microbial interventions, researchers are identifying bioactive metabolites synthesized by gut bacterial cells that can be used as therapeutic compounds. One of the examples of microbial metabolites is urolithins that are microbial derived metabolites of polyphenols and improve mitochondrial function while mitigating inflammation, suggesting their application in metabolic and age-related diseases (Vini *et al.*, 2022). In a similar manner, secondary bile acids and microbial neurotransmitter precursors - GABA, are also being investigated as novel control mechanisms for metabolic and neurological disorders (Pokusaeva *et al.*, 2017).

**Table 2** Key Challenges and Potential Solutions in Metabolomics Research and Clinical Application

Challenges	Description	Possible Solutions	Citations
Lack of Standardized Protocols	Variability in sample collection, processing, and analytical techniques leads to inconsistent results across studies.	Development of universal guidelines, such as those proposed by the MSI, to standardize methodologies for metabolomic research.	(Dunn <i>et al.</i> , 2011)
Inter-Individual Variability in Metabolome	Differences in diet, genetics, medication use, and environmental factors affect metabolomic profiles, leading to inconsistent treatment responses.	Large-scale population studies and AI-driven patient stratification models to identify personalized metabolic signatures and improve precision medicine approaches.	(Zierer <i>et al.</i> , 2018) (Hasin <i>et al.</i> , 2017)
Complexity of Data Interpretation	High-dimensional metabolomics data require advanced computational methods for meaningful interpretation.	Integration of multi-omics approaches, including genomics, transcriptomics, and proteomics, to improve biomarker reliability and provide a systems-level understanding of metabolic pathways.	(Hasin <i>et al.</i> , 2017)
Regulatory Barriers	Lack of clear guidelines for the clinical validation and approval of metabolomics-based diagnostics and therapeutics.	Establishment of regulatory frameworks by agencies such as the FDA to ensure the reproducibility, clinical utility, and safety of metabolomics-based applications.	(Trifonova <i>et al.</i> , 2023)
Limited Clinical Implementation	Despite promising research, metabolomics-based tests and therapies are not widely used in clinical practice.	Increasing collaboration between researchers, clinicians, and industry to translate metabolomics discoveries into clinically validated tools and therapies.	(Wishart, 2019)

Despite promising research, limited clinical implementation remains an obstacle, as metabolomics-based tests and therapies are not yet widely adopted in clinical practice. This gap can be bridged by fostering collaboration between researchers, clinicians, and industry stakeholders to translate metabolomics discoveries into clinically validated tools and therapies (Wishart, 2019). Addressing these challenges through standardization, multi-omics integration, regulatory advancements, and industry partnerships will be key to unlocking the full potential of metabolomics in precision medicine and improving patient outcomes.

**FUTURE DIRECTIONS**

The future of microbiome-based therapeutics is expected to be revolutionized by advancements in metabolomics, paving the way for highly personalized interventions tailored to an individual’s metabolic profile. Over the next 10–20 years, metabolomics will play a crucial role in optimizing dietary recommendations, engineered probiotics, and microbiome-derived pharmaceuticals to enhance therapeutic efficacy. Currently, dietary interventions and probiotics are often applied with a one-size-fits-all approach, leading to inconsistent outcomes due to inter-individual variability in microbiome composition and function (Zeevi *et al.*, 2015). However, metabolomic profiling will enable precision nutrition, allowing clinicians to recommend specific foods, prebiotics, and microbial supplements that enhance beneficial metabolic pathways and modulate disease-related dysbiosis in a targeted manner (Wastyk *et al.*, 2021). This could significantly impact the management of conditions such as metabolic syndrome, IBD, and neurological disorders, where microbiome-metabolite interactions play a crucial role in disease progression. Engineered probiotics represent another promising application of metabolomics-driven microbiome therapeutics. Advances in synthetic biology will allow the development of probiotics designed to produce specific bioactive compounds based on an individual’s metabolic needs. For example, genetically modified *Escherichia coli* or *Lactobacillus* strains could be engineered to secrete butyrate to strengthen gut barrier function in IBD patients or to synthesize neurotransmitter precursors for individuals with gut-brain axis disorders such as depression and anxiety (Olle, 2013). By analyzing an individual’s metabolic profile, clinicians will be able to select the most appropriate engineered probiotic strains, ensuring a personalized and effective intervention. Additionally, microbiome-derived pharmaceuticals will likely emerge as a new class of therapeutics, with researchers identifying novel microbial metabolites with pharmacological properties. Already, compounds such as urolithins—microbial metabolites derived from polyphenols—have demonstrated anti-inflammatory and mitochondrial-enhancing effects, suggesting potential applications in metabolic and aging-related diseases (Vini *et al.*, 2022). Similarly, secondary bile acids and microbial-derived neurotransmitters like GABA could be harnessed for treating metabolic and neurological disorders (Pokusaeva *et al.*, 2017).

Ongoing refinement of AI and ML will also enable further progress in microbiome-metabolomics research. AI algorithms are already being employed to evaluate large, complex datasets for metabolic signatures capable of predicting the risk of developing disease or response to treatment (Chi *et al.*, 2024). Research

applications are expected to shift toward clinical applications within the next twenty years, with AI-driven microbiome analysis potentially enabling real-time metabolomic monitoring to support dynamic treatment adjustments tailored to an individual’s changing metabolic profile (Probul *et al.*, 2024). For example, AI models may help analyze continuous metabolomic data generated by the biosensors and wearable devices, allowing for real-time dietary and therapeutic recommendations tailored to the individual state of one’s microbiome (M. Wang *et al.*, 2022). Real-time fecal metabolomics analysis on smart toilets may facilitate noninvasive monitoring of gut health with prediction of diseases through microbial metabolites (Park *et al.*, 2020). However, their clinical deployment will depend on further technological validation, miniaturization, and standardization. Although the concept is promising, widespread implementation remains in the developmental phase, with pilot studies and prototype models currently shaping their feasibility. This endeavor will enable more precise healthcare delivery, tailored to the individual patient, with the ultimate goal of accelerating the transition to predictive and preventative healthcare from metabolomics data.

To fully realize this vision, continued research into microbial metabolism, standardization of analytical protocols, and robust regulatory frameworks are essential to ensure the clinical validity, reproducibility, and safety of microbiome-targeted therapies. As cost-effective and validated tools become more accessible, metabolomics will occupy a central role in optimizing microbiome-based precision medicine.

**CONCLUSION**

Metabolomics has opened new avenues in microbiome research, providing a distinctive functional angle to microbial performances and their impact on human health. Standard metagenomics provides taxonomical information while in contrast, metabolomics provides insights about active microbial metabolites and their influence on host metabolism, immunity, and the progression of disease. However, the analytical methods such as MS may be the better option for sensitive detection of various microbial metabolites whereas NMR provides reproducibility and structural information. In fact, these advancements have greatly increased our knowledge of microbiome-targeted therapeutics, such as prebiotics, probiotics, postbiotics, and FMT, specifically by helping to elucidate their mechanism of action and increasing the specificity of targeted approaches. The synergy between metabolomics, multi-omics concepts, and AI has also reinforced the status of metabolomics in microbiome-targeted therapeutics through predictive diagnostics and personalized therapeutics design.

Metabolomics, however, has numerous challenges to overcome before it is fully adopted in the clinic. However, there remain critical hurdles including the need for standardization of analytical techniques, overcoming inter-individual variability and establishing regulatory frameworks for microbiome-based interventions. Moreover, more efforts are needed to discover novel microbial metabolites with therapeutic potential and optimize AI-driven strategies of microbiome analysis. Bridging these gaps will be critical for the microbiome-metabolomics research to yield effective, reproducible, and clinically relevant applications.

Looking ahead, the future of microbiome-based therapeutics lies in the development of highly personalized interventions tailored to an individual's metabolic profile. Advances in engineered probiotics, microbiome-derived pharmaceuticals, and AI-driven predictive modeling will enable precision medicine approaches that optimize gut health and prevent disease. As research continues to uncover the intricate connections between microbial metabolism and human physiology, metabolomics will play a central role in unlocking novel therapeutic possibilities. Ultimately, this field has the potential to revolutionize healthcare by providing innovative, personalized solutions for a wide range of metabolic, inflammatory, and neurological disorders, improving human health on a global scale.

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