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Review Article

Artificial Intelligence-Driven Reconstruction of Host–Microbiome Metabolic Networks: From Multi-Omics Integration to Precision Medicine

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ABSTRACT

The human microbiome functions as a metabolically active organ whose biochemical output is continuously integrated with host physiology. Conventional microbiome surveys, built largely on taxonomic profiling, capture community composition and diversity but resolve neither the functional capacity of these communities nor the bidirectional metabolic exchange that links them to the host. A central limitation is that taxonomy is a poor proxy for function: phylogenetically distinct organisms can perform equivalent reactions, and closely related taxa can diverge metabolically. Resolving host-microbiome interactions, therefore, requires integration across heterogeneous, high-dimensional molecular layers, such as metagenomics, metatranscriptomics, proteomics, metabolomics, and host genomic and phenotypic data at a scale and complexity that exceeds classical analytical pipelines. This narrative review aims to examine how artificial intelligence-driven integration of multi-omics data supports the reconstruction of host-microbiome metabolic networks and its implications for precision medicine. This narrative review provides a comprehensive conceptual synthesis of current evidence regarding artificial intelligence-driven reconstruction of host–microbiome metabolic networks. Relevant literature was identified iteratively from seminal publications, peer-reviewed research articles, and authoritative reviews and synthesized narratively to evaluate recent advances, translational applications, current challenges, and future directions in this rapidly evolving field. Machine learning, deep learning, and graph-based models can integrate multi-omics data, infer latent metabolic structure, and predict microbial functional potential. They can also model microbe-metabolite-host relationships as connected networks rather than isolated components. These approaches have facilitated the discovery of disease-associated microbial and metabolic signatures and candidate therapeutic targets, and they underpin emerging precision medicine applications, including individualized risk stratification, biomarker discovery, and treatment response prediction. Substantial barriers remain, however, including incomplete and non-standardized reference data, limited model interpretability, vulnerability to bias and overfitting, and a shortage of prospective clinical validation. Continued progress in foundation models, real-time microbiome monitoring, and patient-specific metabolic modelling is expected to move the field from descriptive association toward predictive, preventive, and personalized clinical application.

Keywords: Artificial Intelligence; Host-Microbiome Interactions; Metabolic Networks; Multi-Omics Integration; Precision Medicine

Introduction

The human microbiome is now recognized not as a passive collection of commensal organisms but as an active participant in host physiology. The gastrointestinal microbiota, in particular, behaves as a metabolic organ that contributes to nutrient processing, energy harvest, immune education, and the maintenance of metabolic homeostasis. Microbial communities engage the host through a dense web of biochemical reactions, generating bioactive metabolites from dietary and endogenous substrates that act locally in the gut and at distant sites in organs. This understanding has shifted the central question of microbiome research from who is present to what the community does, from cataloguing composition to mapping the functional metabolic networks that connect microbes to host health and disease(1,2).

Host-microbe communication is inherently bidirectional. Host-derived conditions, nutrient availability, pH, bile flow, and immune tone shape microbial community structure, while the community in turn supplies metabolic functions absent from the human genome. Much of this dialogue is mediated by defined classes of microbial metabolites: short-chain fatty acids (SCFAs), secondary bile acids, tryptophan catabolites such as indole derivatives, and trimethylamine N-oxide (TMAO), which collectively influence immune regulation, energy metabolism, epithelial integrity, and disease progression (3–5). Yet taxonomic surveys alone often fail to explain this functional variation, because metabolic output is not reliably predicted by community membership. Functionally redundant pathways are distributed across unrelated taxa, and similar communities can behave differently under different host conditions. Compounding this, the host- microbiome relationship is governed by signals spread across multiple molecular layers, whose joint interpretation lies beyond the reach of conventional, single-omic analysis.

Artificial intelligence (AI) offers a complementary paradigm for reconstructing and interpreting host-microbiome metabolic systems. Machine learning and deep learning can detect structure in large-scale biological datasets, predict the functional repertoire of microbial communities, and relate microbial activity to host pathways. Network-based methods, particularly graph representations, are especially well-suited to biology, because they model interacting microbes, genes, metabolites, and host pathways as connected systems rather than independent variables (3,4,6,7). By coupling multi-omics integration with computational modelling, AI-driven reconstruction of host-microbiome metabolic networks has emerged as a promising systems-level approach for investigating disease mechanisms, biomarker discovery, and targeted therapeutic interventions(8,9). This review surveys that emerging field, tracing the progression from descriptive microbiome analysis toward predictive, personalized, microbiome-informed precision medicine. We outline the architecture of host microbiome metabolic networks, the multi-omics foundation required to reconstruct them, the principal AI methodologies now applied to the task, their translational applications, and the methodological and clinical barriers that must be overcome. Across these sections we synthesize current evidence into a unifying conceptual framework, summarized in Figure 1, in which multi-omics inputs, AI-based modelling, network reconstruction, and clinical application form a single continuous translational pipeline rather than a set of disconnected analyses.

Methodology

Study Design

This study was conducted as a narrative review to provide a comprehensive synthesis of current evidence on artificial intelligence (AI)-driven reconstruction of host–microbiome metabolic networks and their emerging applications in precision medicine. Unlike a systematic review, the narrative review approach was selected to integrate findings from diverse areas of research, including microbiome science, systems biology, multi-omics technologies, machine learning, metabolic network modelling, and translational medicine, thereby providing a broad conceptual perspective on this rapidly evolving interdisciplinary field.

As this study was designed as a narrative review rather than a systematic review, no formal systematic search protocol, PRISMA flow diagram, or quantitative study selection process was undertaken. Instead, the review aimed to provide a critical and integrative synthesis of the current body of knowledge on the topic.

Literature Identification

This narrative review was developed through an iterative identification and evaluation of relevant scientific literature on artificial intelligence (AI)-driven reconstruction of host–microbiome metabolic networks and precision medicine. Rather than following a predefined systematic search protocol, the literature was identified progressively throughout the

preparation of the manuscript. Key publications were located through references cited in influential review articles, seminal primary research papers, authoritative books, conference proceedings, and recommendations from the broader scientific literature. Additional relevant publications were incorporated as new concepts and emerging themes were identified during manuscript development to ensure comprehensive coverage of this rapidly evolving interdisciplinary field.

Study Selection and Eligibility Criteria

Publications were selected based on their scientific relevance, methodological quality, and contribution to the major themes addressed in this review, including host–microbiome metabolic interactions, multi-omics integration, artificial intelligence methodologies, metabolic network reconstruction, and precision medicine. Priority was given to peer-reviewed original research articles, landmark studies, methodological papers, high-quality review articles, and consensus publications published in reputable scientific journals. Publications that did not substantially contribute to the conceptual scope of the review were not considered further. Because this study was conducted as a narrative review, no formal study screening process, predefined record counts, or quantitative study selection workflow was undertaken.

Data Extraction and Narrative Synthesis

Information from the selected publications was examined critically and synthesized narratively according to the major thematic areas addressed in this review. Evidence relating to host–microbiome metabolic interactions, multi-omics technologies, artificial intelligence approaches, metabolic network reconstruction, clinical applications, current limitations, and future research directions was integrated to provide a comprehensive conceptual overview of the field. Figures and tables were developed by the authors through synthesis of evidence from the cited literature and are intended to summarize current knowledge rather than present the results of a systematic evidence synthesis.

Architecture of Host–Microbiome Metabolic Networks

Components of Host–Microbiome Metabolic Interactions

Host–microbiome metabolic interactions constitute a continuously coupled network of biochemical exchange, in which a metabolite produced by one organism or system serves as a substrate, signal, or regulator for another. The host and its microbiota are best understood not as separate metabolic systems but as a single integrated ecosystem. Characterizing this ecosystem requires moving beyond species identification toward understanding how metabolic labour is partitioned and coordinated across the community and the host.

Microbial pathways substantially extend the biochemical repertoire of the human system. Many microorganisms encode enzymes that are absent or expressed at much lower levels in humans, thereby enabling the breakdown of complex dietary polysaccharides, the synthesis of bioactive compounds, and the biotransformation of host- and diet-derived molecules. These activities are not incidental: SCFAs derived from microbial fermentation support epithelial barrier integrity, immune regulation, and energy homeostasis, while microbial conversion of primary to secondary bile acids modulates host signalling through receptors such as FXR and TGR5, with downstream effects on lipid metabolism, glucose handling, and immunity (3,10). Host metabolism, in turn, regulates microbial function by setting the nutrient and chemical environment in which the community operates.

Within the community, interactions are both cooperative and competitive. Cooperation is exemplified by metabolic cross-feeding, in which the products of one taxon become substrates for another. For instance, primary degraders liberate intermediates from complex carbohydrates that are subsequently fermented to SCFAs by secondary consumers (11–13). Such exchange stabilizes community structure and functional output. Competition, by contrast, arises when organisms contend for shared nutrients, niches, or limiting cofactors, shaping both the abundance and composition of the community and, consequently, the metabolic output of the entire ecosystem. The net behaviour of the system is therefore an emergent property of these interactions rather than a sum of individual capacities.

Metabolic Network Reconstruction Approaches

To formalize this complexity, computational methods reconstruct metabolic networks from molecular data. The most established approach is the genome-scale metabolic model (GEM), which represents the full metabolic potential of an organism inferred from its genome. GEM construction maps metabolism-associated genes to biochemical reactions and links those reactions into coherent pathways (14,15). Automated reconstruction now makes community-scale modelling feasible: genome-scale models can be generated semi-automatically with tools such as CarveMe and gapseq, curated resources such as AGORA and AGORA2 provide pre-built

reconstructions for hundreds of human gut strains, and platforms such as KBase support reproducible reconstruction workflows (16–20).

Flux balance analysis (FBA) is a principal analytical method applied to GEMs. As a constraint-based technique, FBA estimates the flow of metabolites through a reaction network under defined constraints, nutrient availability, reaction bounds, and an assumed cellular objective to predict feasible metabolic states (15). Applied to microbiome data, GEMs and FBA can predict metabolite production, probe community-level interactions, and estimate the metabolic consequences of compositional change. Community-aware extensions such as MICOM and SteadyCom model inter-species exchange and community- level flux explicitly, allowing cross- feeding and metabolic competition to be captured within a single framework (21,22).

These methods have clear limitations. GEM accuracy depends heavily on genome annotation quality and prior biochemical knowledge; incomplete reference databases, uncharacterized genes, and unknown reactions degrade reliability, particularly for poorly studied taxa. Constraint- based models are also simplified, often static representations that do not capture the temporal dynamics of microbial communities or their dependence on host physiology and environment. Emergent behaviours of multi species ecosystems are correspondingly difficult to predict with conventional models (15,18).

The Case for AI-Enhanced Reconstruction

These constraints motivate computational approaches that can incorporate richer, less explicitly specified biological information. AI has the potential to strengthen metabolic network reconstruction by learning patterns within large, intricate datasets that may not be readily discernible through annotation-driven methods alone. Machine learning can relate microbial genomic features, metabolomic profiles, and host phenotypes, improving the prediction of microbial metabolic function and disease-associated changes (23,24).

A key advantage is the capacity to integrate high-dimensional multi-omics data-including metagenomics, metatranscriptomics, proteomics, and metabolomics -jointly rather than analysing each layer independently, yielding more robust representations of host-microbiome interactions. Deep learning and network-based methods are particularly effective at capturing the nonlinear, context-dependent relationships among microbes, metabolites, genes, and host pathways (25,26). In doing so, AI-driven reconstruction reframes host microbiome systems as dynamic, predictive networks. This shift from static modelling to data-driven network inference represents an important step towards precision medicine, in which individual microbial and metabolic profiles, rather than population averages, may inform disease prediction, prevention, and therapy.

Multi-Omics Integration for Host–Microbiome Systems Biology

Because microbial communities are embedded in a tightly interconnected biological environment spanning genes, transcripts, proteins, metabolites, and host physiology, single-omic analysis cannot fully describe their function. Multi-omics integration assembles information across molecular levels into a more complete picture of microbial activity and its host consequences (27). This systems biology perspective is particularly valuable because compositional shifts do not necessarily correspond to functional or biological consequences; functional inference requires evidence from the molecular layers at which metabolism is actually executed.

Types of Multi-Omics Data

Metagenomics is foundational, characterizing the genetic composition of a community through DNA sequencing. It identifies the taxa present and predicts their functional potential, revealing pathways for processes such as carbohydrate degradation, amino acid metabolism, and biosynthesis of microbial bioactive compounds (28). Because metagenomics measures genetic potential rather than realized activity, additional molecular layers are required to determine whether predicted functions are actually expressed. Metatranscriptomics reports active gene expression; proteomics and metabolomics provide direct evidence of enzymatic activity and metabolic output; and host genomic and epigenomic data explain individual variation in microbiome composition and response. The complementary contribution of each layer to network reconstruction is summarized in Table 1.

Table 1. Omics data layers enabling host–microbiome metabolic network reconstruction.

Omics layer	Information generated	Representative tools/methods	Contribution to network reconstruction
Metagenomics	Microbial taxonomic composition and functional gene content	MetaPhlAn, Kraken2, HUMAnN	Defines metabolic potential and predicts candidate biochemical pathways(29)
Metatranscriptomics	Active microbial gene expression profiles	HUMAnN, SAMSA2	Identifies which pathways are actively expressed under given conditions(29)
Metabolomics	Microbial- and host-derived metabolites	XCMS, MS-DIAL, MetaboAnalyst	Supplies functional evidence of activity and host–microbial chemical signalling(30)
Proteomics	Protein abundance and enzyme activity	MaxQuant, MetaProteomeAnalyzer	Confirms active metabolic processes and molecular responses(31,32)
Host genomics/epigenomics	Host genetic variation and regulatory state	GATK, PLINK, EWAS pipelines	Explains individual differences in composition and metabolic response(33)

EWAS, epigenome-wide association study; GATK, Genome Analysis Toolkit; HUMAnN, The HMP Unified Metabolic Analysis Network; MS-DIAL, Mass Spectrometry–Data Independent AnaLysis; PLINK, Whole Genome Association Analysis Toolset; SAMSA2, Simple Annotation of Metatranscriptomes by Sequence Analysis 2; XCMS, XCMS metabolomics data processing platform.
Source: *Synthesized by the authors from the cited literature (29–33).*

Artificial Intelligence-Based Reconstruction of Host–Microbiome Metabolic Networks

Reconstructing host-microbiome metabolic networks is among the hardest problems in systems biology: a large number of interacting taxa with distinct metabolic capacities continuously shape host physiology. Classical computation has yielded important insight but generally depends on prior biological knowledge and simplifying assumptions that underrepresent the adaptability and context dependence of microbial ecosystems. AI has emerged as a promising approach to addressing these challenges by integrating multi-omics data at scale, learning complex biological relationships, and enabling predictive modelling of metabolic interactions, allowing host microbiome systems to be analysed as dynamic networks rather than collections of isolated pathways (25,26).

AI-Driven Metabolic Pathway Prediction

A major application is predicting the metabolic potential of microbes from genomic and multi-omics data. Although metagenomic sequencing provides extensive gene-level information, translating gene content into functional prediction is non-trivial because gene presence does not guarantee expression or metabolic activity. AI can improves this inference by learning relationships among genomic features, annotated pathways, and experimentally confirmed functional outcomes (18,23).

Machine learning models can detect patterns in microbial genomic data to predict pathway abundance and metabolite production, and deep learning extends this by capturing gene-protein and biochemical network relationships without requiring them to be specified in advance. Such methods are especially valuable for poorly characterized organisms, where annotation-driven prediction performs poorly (25,34). AI can also generate hypotheses about the function of uncharacterized microbial genes from sequence similarity, predicted structure, and network context, and can combine genomic and metabolomic evidence to reconstruct pathways and anticipate their impact on host biology.

Machine Learning for Interaction Mapping

Host-microbiome metabolic systems depend on interactions among microbes and between microbes and host tissues. Machine learning provides tractable ways to infer these relationships from the large datasets generated by sequencing, metabolomics, and clinical measurement (35,36).

One important application is the prediction of microbial interactions. Because community members compete for nutrients, exchange metabolic products, and regulate one another through chemical signals, patterns of co-abundance and metabolite production can be used to infer probable cooperative or

competitive relationships, information that is central to understanding community dynamics in health and disease. A second application is microbe-host metabolite exchange: by integrating microbial genomic, host metabolomic, and clinical data, models can be used to associate specific microbial activities with host metabolic phenotypes, helping to identify mechanisms by which microbiome alterations contribute to disease (26,37).

Machine learning has been applied to identify disease-associated microbial and metabolic signatures across conditions, including inflammatory bowel disease, type 2 diabetes, colorectal cancer, and cardiovascular disease, supporting both biomarker discovery and mechanistic investigation (6,38–42). A crucial caveat applies throughout: associations recovered by AI require biological validation before clinical translation. Correlation does not establish causation, and mechanistic understanding remains essential to interpret any inferred relationship.

These approaches are complementary. Machine learning is used primarily for pattern recognition and prediction, whereas deep learning and network-based methods model the more complex relationships among microbes, metabolites, genes, and host pathways. The principal AI approaches and their applications synthesized from the current literature are summarized in Table 2.

Table 2. Artificial intelligence approaches for host–microbiome metabolic network reconstruction and precision medicine.

AI approach	Principle	Application in host–microbiome research
Random forests	An ensemble of decision trees aggregating multiple partitions of the data	Disease classification and microbial biomarker identification
Support vector machines	Supervised classification of complex, high-dimensional data	Detection of disease associated microbial signatures
Gradient boosting	Sequential refinement of weak predictive models	Prediction of metabolic phenotypes and clinical outcomes
Neural networks	Modelling of non-linear relationships in biological data	Multi-omics integration and functional prediction
Autoencoders	Unsupervised feature extraction and dimensionality reduction	Discovery of latent structure in high-dimensional datasets
Graph neural networks	Learning over interconnected biological graphs	Prediction of microbial interactions, metabolic relationships, and network behaviour

Abbreviations: *AI, artificial intelligence.*

Source: *Synthesized by the authors from published evidence cited throughout the manuscript, particularly Refs.* ***23–26, 34–42.***

Graph-Based AI Models for Metabolic Networks

Because host-microbiome interactions involve many interdependent components, graph-based AI is a natural fit for network reconstruction. In a graph, nodes represent biological entities and edges represent the relationships between them, an abstraction that mirrors biological systems, in which microbes, genes, metabolites, and host pathways interact in complex ways (26,43).

In a host-microbiome metabolic network, nodes may denote microbial species, microbial genes, metabolites, or host-molecular pathways, while edges encode metabolic conversions, molecular interactions, metabolite exchange, or regulatory relationships. This representation allows models to reason about system architecture and connectivity rather than individual parts in isolation. Graph neural networks (GNNs) are particularly compelling because they propagate information across connected structures: unlike methods that treat variables as independent, GNNs incorporate network context into prediction, which suits systems in which a component's function depends on its interactions (43). In host-microbiome research, graph-based models can improve prediction of metabolic interactions, highlight key regulatory pathways, and identify microbial or molecular factors that influence disease mechanisms, thereby offering a principled way to fuse heterogeneous biological evidence into a coherent network.

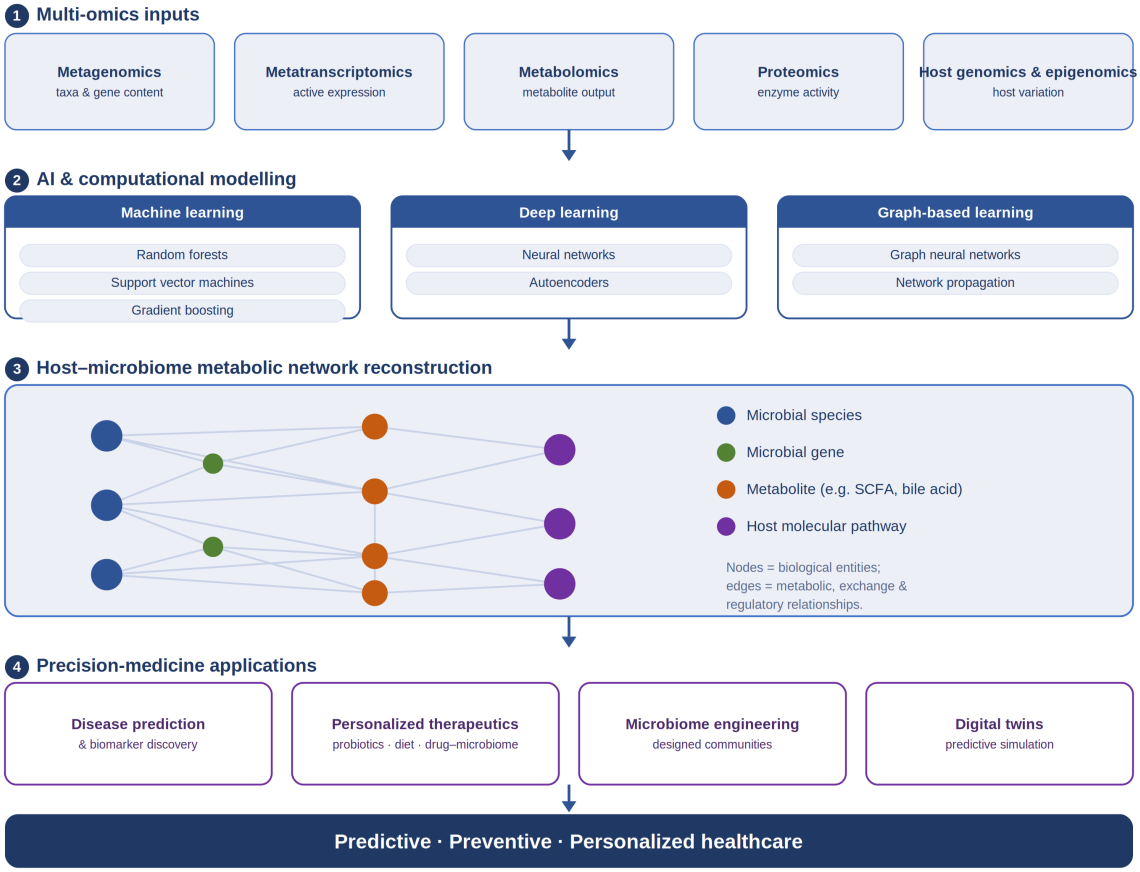

Figure 1. Evidence-informed conceptual framework illustrating AI-driven reconstruction of host-microbiome metabolic networks and its translation to precision medicine.

Multi-omics inputs (Stage 1) are integrated by machine learning, deep learning, and graph-based methods (Stage 2) to reconstruct host-microbiome metabolic networks in which nodes represent biological entities microbes, microbial genes, metabolites, and host pathways and edges represent metabolic, exchange, and regulatory relationships (Stage 3). The resulting networks support precision medicine applications, including disease prediction and biomarker discovery, personalized therapeutics, microbiome engineering, and digital twin simulation (Stage 4), collectively enabling a shift toward predictive, preventive, and personalized care. The framework was developed by the authors through synthesis of current evidence from the cited literature and is intended as a conceptual representation of AI-enabled host-microbiome metabolic network reconstruction rather than a validated computational model.

Digital Twins and Predictive Microbiome Modelling

Microbiome digital twins- AI-driven, individualized simulations of how a person's microbiome behaves under defined conditions remain at an early stage but represent a promising direction. Such models would combine host characteristics, microbiome composition, and metabolic data into personalized representations of host microbial interaction (21).

In principle, digital twins could predict an individual's response to microbiome targeted interventions such as dietary change, probiotics, or pharmacotherapy, and could be used to simulate community responses before an intervention is applied supporting individualized risk assessment and outcome prediction. Realizing this vision depends on overcoming substantial obstacles in data availability, model interpretability, and clinical validation, discussed in Section 6.

Applications in Precision Medicine

Coupling AI with host microbiome metabolic network analysis opens new opportunities for precision medicine. Whereas conventional treatment is often guided by population level disease categories, patients differ substantially in genetics, microbial load, metabolism, and drug response. By integrating

microbial, metabolic, and clinical data, AI-driven microbiome analysis provides a framework for recognizing clinically meaningful patterns in an individual's biology, with the potential to improve disease prediction, support biomarkers, and inform targeted intervention (44,45).

Disease Prediction and Biomarker Discovery

A primary application is the discovery of microbial biomarkers of health and disease. Microbial communities exhibit complex patterns that single taxon analyses may miss; machine learning can mine large microbiome datasets to identify combinations of taxa, genes, and metabolic features that distinguish disease from health. Such signatures hold promise for early detection and risk assessment, though they are highly context-dependent and require validation across diverse populations and clinical settings (35,41).

In oncology, AI-driven analyses have helped associate microbiome patterns with specific cancers and with treatment response, including modulation of the tumour microenvironment and of responses to immunotherapy (46–48). Because these signatures are strongly context-dependent, cross-cohort validation is essential. In metabolic disease, shifts in gut microbial composition and activity have been linked to obesity and type 2 diabetes; AI models can integrate microbial abundance, functional gene content, and metabolite concentrations to detect metabolic patterns associated with disease progression (49,50). Systems-level analysis is especially valuable here, since metabolic disease reflects the combined influence of microbial activity, host metabolism, diet, and environment.

Beyond composition, AI can detect metabolic signatures that reflect functional change in the host-microbiome system. Metabolites such as SCFAs and secondary bile acids may provide more direct evidence of biological activity than abundance alone; integrating metabolomic and microbiome data, therefore, allows models to uncover metabolic patterns associated with disease onset and progression (35,41).

Personalized Therapeutic Strategies

AI-based microbiome analysis is increasingly directed toward personalized therapy. One emerging application is precision probiotics: computational selection of strains- likely to benefit a particular individual. By accounting for interindividual variation in microbiome composition, metabolic potential, and disease features, such models aim to predict probiotic effects more accurately than a one-strain-for-all approach.

Similarly, AI can support personalized dietary guidance by forecasting how dietary components affect microbial metabolism. Although diet strongly shapes community structure, individual responses vary considerably; models trained on microbiome and metabolic profiles can, in principle, generate individualized dietary recommendations (51). A further priority is the interaction between the microbiota and pharmaceuticals. Microbial enzymes can modify drugs, influencing activation, bioavailability, efficacy, and toxicity; integrating AI with microbiome and pharmacological data could help predict drug-microbiome interactions and identify patients whose treatment response is likely to be microbiome-modulated important step toward safer, more individualized therapy (52,53).

Microbiome Engineering

Beyond prediction and analysis, AI is contributing to microbiome engineering, which seeks to design or manipulate microbial communities for therapeutic benefit. Synthetic biology has enabled the construction of engineered microbes that produce useful metabolites, modulate immunity, or target disease pathways, but predicting their behaviour within complex ecosystems remains difficult, given the many interdependent, context-dependent interactions involved (54).

AI-driven approaches can help by modelling microbial interactions, predicting metabolic outcomes, and identifying combinations of organisms most likely to achieve a desired therapeutic effect. Machine learning and network-based models may also help assess the ecological stability and safety of engineered communities before clinical use. Although microbiome engineering remains early-stage, the convergence of synthetic biology, AI, and metabolic modelling represents a promising route to next-generation microbiome-based therapeutics (55).

Current Challenges and Limitations

Despite clear progress, several obstacles limit the translation of AI-driven host microbiome reconstruction into reliable biological and clinical applications. These span the intrinsic complexity of microbial ecosystems, the limitations of available data, methodological challenges specific to AI, and barriers to clinical implementation. Together, they define the principal knowledge gaps the field must close, and we frame each below as a priority target for future research.

Biological Complexity

The biological complexity of the host microbiome system is itself a central challenge to predictive modelling. Gut microbiota composition varies markedly with genetics, age, geography, diet, lifestyle, medication, and environment, so a microbial

signature associated with a disease in one population may not carry the same biological meaning in another. This variability complicates the development of universal biomarkers and underscores the need to incorporate individual-specific factors into models (4,56).

The microbiome is also dynamic, changing in composition and activity in response to diet, infection, medication, and physiological state. Cross-sectional studies capture a single time point and may not represent long-term behaviour or response to disease progression and therapy. Longitudinal designs that track the microbiome over time are therefore important for building accurate predictive models (38).

Data Limitations

Effective AI depends on high-quality data. Multi-omics technologies generate large volumes of microbiome data, yet current reference resources remain incomplete: the functions of many microbial genes and metabolic pathways are poorly characterized, especially for understudied taxa, limiting the accuracy of functional prediction (57).

A second constraint is the lack of standardization across microbiome studies. Differences in sampling, sequencing, processing, and analysis pipelines introduce batch effects that undermine reproducibility and cross-study comparison. Many available datasets are also relatively small and inadequately representative of demographic and environmental diversity. Finally, the scarcity of longitudinal multi-omics studies impedes understanding of how host-microbiome metabolic networks change over time; richer data linking composition, metabolic activity, host response, and clinical outcome are needed to improve predictive accuracy (35).

AI-Related Challenges

AI also introduces methodological challenges. Interpretability is foremost: many high performing methods, particularly deep learning models, do not readily expose the biological logic underlying their predictions. In biomedicine, this is a serious limitation, because clinical decisions must be biologically justified as well as accurate n(25).

A second major challenge is overfitting, in which models perform well on training data but fail to generalize to independent datasets. This problem is particularly pronounced in microbiome research because biological variables are numerous while sample sizes are often limited. Rigorous validation on independent populations is essential. A third challenge is algorithmic bias. AI models may inherit biases present in their training data, which can reduce their ability to generalize across diverse populations, healthcare settings, and clinical contexts. Most AI based microbiome models remain at the research stage and require comprehensive clinical testing before routine use(35). Beyond technical performance, effective implementation of AI in host–microbiome research requires appropriate human oversight throughout model development, validation, and clinical application. AI-generated predictions should complement, rather than replace, expert clinical judgment, particularly when informing diagnostic, prognostic, or therapeutic decisions. Transparent model development, rigorous external validation, continuous performance monitoring, and interdisciplinary collaboration among clinicians, microbiologists, bioinformaticians, and data scientists are essential to ensure that AI-assisted decision-making remains accurate, interpretable, ethically responsible, and clinically accountable. Establishing appropriate regulatory frameworks and governance mechanisms will also be important for promoting trust and facilitating the safe integration of AI into precision medicine.

Translation into Clinical Practice

Moving AI microbiome tools from laboratory to clinic raises additional hurdles. Regulatory approval requires robust evidence of safety, accuracy, and clinical utility, which is complicated by the biological complexity and inter-individual variability of microbiome-based interventions (45,58).

Reproducibility is equally critical: models must perform consistently across laboratories, populations, and healthcare settings, which in turn demands standardized protocols for generating and analysing microbiome data. Finally, clinical integration will require sustained collaboration among computational scientists, microbiologists, clinicians, and regulators. Human oversight should remain central throughout AI-assisted clinical decision-making to ensure that model outputs are interpreted within the appropriate biological and clinical context. In addition, AI tools must integrate seamlessly into existing clinical workflows and provide transparent, interpretable outputs that clinicians can readily evaluate and act upon. Whether AI-driven host microbiome reconstruction matures from a research methodology into a component of precision medicine will depend on addressing these challenges.

Future Perspectives

Progress in host-microbiome metabolic systems will be shaped by continued advances in AI, multi-omics technology, and computational biology. Current models already detect microbial functions, interactions, and disease patterns; the next generation will need to be more comprehensive, adaptable, and clinically relevant, moving microbiome research from retrospective description toward predictive, personalized application.

Foundation Models and Generative AI

A key direction is the application of foundation models and generative AI to microbiome systems biology. As in other domains, biological foundation models trained on large corpora biological sequences, molecular interactions, and multi-omics data may improve the prediction of microbial function, reconstruction of metabolic pathways, and identification of links between microbial activity and host physiology (59,60). Generative approaches could additionally mine large datasets to propose candidate mechanisms for experimental testing. Such systems should augment rather than replace experimental research, helping investigators identify previously unrecognized metabolic pathways and prioritize hypotheses; their value will depend on training data quality, biological validation, and careful interpretation of outputs.

Real-Time Microbiome Monitoring

Wearable biosensors and advanced metabolite detection technologies may eventually enable real-time monitoring of host microbiome interactions. In contrast to single-time point-measurement, continuous monitoring could capture dynamic changes in microbial activity linked to diet, medication, disease management, and therapy. Substantial technical hurdles remain, but advances in sensing and computational analysis could support more accurate, individualized health management (61,62).

Personalized Metabolic Modelling

A long-term goal is the development of patient-specific metabolic models that integrate microbiome composition, metabolism, and host biology. Such models could improve the prediction of disease risk, treatment response, and outcomes following dietary or pharmacological intervention, supporting a shift from reactive care toward preventive and predictive medicine through early detection of metabolic change and individualized treatment. Achieving this will require large longitudinal datasets, greater model transparency, and close collaboration between computational and clinical researchers (19,21).

Conclusion

Artificial intelligence offers a transformative framework for understanding host microbiome metabolic interactions, enabling integration, analysis, and interpretation of large-scale biological data. In contrast to traditional approaches that examine microbial components in isolation, AI-driven strategies allow host and microbial systems to be studied as interconnected metabolic networks. By integrating multi-omics data—including metagenomics, metatranscriptomics, proteomics, metabolomics, and host molecular information—these approaches provide a more complete account of how microbial activity shapes human physiology and disease. The growing capacity of AI to reconstruct metabolic networks, identify functional microbial signatures, and predict biological interactions has created promising opportunities for precision medicine, with the potential to improve disease prediction, biomarker discovery, and personalized therapy. Clinical translation, however, will require careful attention to incomplete reference data, limited interpretability, potential bias, and the need for rigorous prospective validation. Continued progress will depend on interdisciplinary collaboration among computational scientists, microbiologists, clinicians, and experimentalists. Addressing these challenges could establish AI-driven host microbiome metabolic network reconstruction as a foundation for predictive, preventive, and personalized healthcare.

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