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Synergizing multi-omics and artificial intelligence to unravel gut microbiome complexity: A review

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Abstract

The integration of multi-omics technologies with advanced artificial intelligence (AI) and machine learning (ML) frameworks has transformed gut microbiota research into a predictive, mechanistic, and precision-driven discipline. The gut microbiome, a complex ecosystem that influences metabolism, immune function, barrier integrity, and neuroendocrine signaling, generates massive datasets through metagenomics, meta-transcriptomics, metaproteomics, metabolomics, and host interaction omics. Traditional analytical tools are limited in their ability to address the nonlinear, high-dimensional, and heterogeneous nature of microbiome datasets. AI-empowered approaches—including classical ML algorithms, deep learning architectures, graph neural networks, reinforcement learning, and explainable AI—enable sophisticated pattern discovery, microbial biomarker identification, ecological interaction mapping, and causal inference. These computational strategies facilitate multi-modal data fusion, latent-space modeling, and the development of digital gut twins that simulate host–microbe interactions and predict personalized therapeutic responses. AI-integrated multi-omics frameworks have shown substantial impact across metabolic disorders, cancer immunotherapy, neurodegenerative diseases, gastrointestinal diseases, and infection biology. Emerging opportunities include AI-enabled microbiome drug discovery, clustered regularly interspaced short palindromic repeats-based microbial engineering, organoid–AI platforms, and single-cell microbiomics, offering unprecedented resolution into microbe–host dynamics. However, challenges persist in data standardization, interpretability, privacy, cross-population generalizability, and regulatory validation. Addressing these limitations through interoperability, Findable–Accessible–Interoperable–Reusable data principles, federated learning, and mechanistically grounded biomarkers will be essential for clinical translation. Altogether, the convergence of multi-omics and AI heralds a new era of microbiome science, enabling precision diagnostics, personalized nutrition, rational probiotic design, and predictive microbiome therapeutics that will reshape future healthcare ecosystems.

Keywords: Gut microbiota; Multi-omics integration; Artificial intelligence; Machine learning; Digital gut twin; Microbiome biomarkers

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1. Introduction

The gut microbiota constitutes a dense and dynamic microbial ecosystem essential for metabolic regulation, immune maturation, epithelial barrier function, and neuroendocrine communication. Accumulating evidence implicates microbial dysbiosis in metabolic disorders, inflammatory bowel disease (IBD), colorectal cancer, neurological disorders, and autoimmune pathologies.[1] Advances in sequencing, computational biology, and experimental models have transformed microbiome science from descriptive taxonomy into a systems-level discipline integrating ecological, metabolic, immunological, and clinical dimensions. The rapid emergence of high-resolution, multi-omics platforms generates large-scale data requiring robust analytical frameworks.[1,2] However, the complexity, heterogeneity, compositionality, and longitudinal nature of microbiome datasets limit the capabilities of traditional statistical tools. Artificial intelligence (AI) and machine learning (ML) address these challenges by uncovering latent patterns and modeling nonlinear microbial–host interactions. Thus, the convergence of multi-omics and AI represents a key frontier in precision microbiome medicine.[3]

Beyond its fundamental physiological functions, the gut microbiome has emerged as a critical determinant of modern healthcare strategies, influencing disease prevention, diagnosis, and therapeutic interventions.[4] Microbiome-based biomarkers are increasingly being explored for early disease detection, risk stratification, and prediction of treatment response, while therapeutic modulation through probiotics, prebiotics, postbiotics, dietary interventions, and fecal microbiota transplantation is gaining clinical relevance.[5] Moreover, inter-individual variability in microbiome composition contributes to heterogeneous drug responses and adverse effects, underscoring its importance in precision and personalized medicine. These developments highlight the microbiome as a modifiable target with significant translational potential in contemporary healthcare systems.[6]

1.1. Gut microbiota: A systems biology perspective

The gut microbiota functions as a metabolic and immunological organ composed of trillions of microbes that encode a gene repertoire far exceeding that of the human genome. Systems-biology frameworks reveal multi-layered host–microbe interactions influencing nutrient metabolism, immune tolerance, gut barrier homeostasis, neurotransmitter synthesis, and endocrine signaling.[2,3] Short-chain fatty acids (SCFAs), bile acids, tryptophan metabolites, and microbial neuroactive molecules modulate host pathways and neuroimmune networks.[7] Perturbations in microbial structure or function—dysbiosis—are linked to cardiometabolic disease, colorectal cancer, neuropsychiatric disorders, and autoimmune pathologies.[8] The systems-level nature of these interactions necessitates integrated analyses across microbial communities, metabolic networks, and immune signaling to elucidate causal mechanisms driving health and disease.[9]

1.2. Emergence of multi-omics in microbiome research

Technological advances have transformed microbiome science into a multi-omics discipline. Metagenomics enables species- and strain-level functional gene discovery, while meta-transcriptomics reveals context-dependent microbial expression dynamics.[10] Metabolomics and metaproteomics can identify microbial metabolites and enzymes that shape host physiology, including SCFAs, bile acids, neurotransmitters, antimicrobial peptides, and inflammatory mediators.[11] Host single-cell omics, spatial transcriptomics, and immune-profiling technologies can delineate mucosal immune–microbe interactions.[12] Integrative pipelines can now reconstruct functional ecological networks, metabolic fluxes, immune responses, and host signaling dynamics.[13] Despite these advances, multi-omics datasets remain large-scale, sparse, compositional, and noise-prone, requiring advanced computational approaches for integration and inference.[14]

1.3. Role of artificial intelligence and machine learning

Artificial intelligence and ML approaches provide robust solutions for decoding the complexity of the microbiome. Classical models such as random forests, support vector machines, and regularized regression can identify microbial biomarkers, disease signatures, and host–microbe associations.[15] Deep learning frameworks, including convolutional neural networks, recurrent neural networks (RNNs), graph neural networks (GNNs), and transformers, enable the extraction of latent representations across multi-omics layers, capturing nonlinear interactions and ecological dependencies.[9,16] Graph-based learning models elucidate microbe–metabolite and host immune networks, while generative models (variational autoencoders [VAEs] and generative adversarial networks) support microbiome simulation, denoising, and synthetic augmentation.[17] Emerging digital gut twin systems integrate mechanistic metabolic models and ML for individualized dietary, probiotic, and therapeutic optimization.[18] However, challenges persist in reproducibility, interpretability, batch correction, and regulatory acceptance, requiring ethical and computational rigor for clinical translation. Figure 1

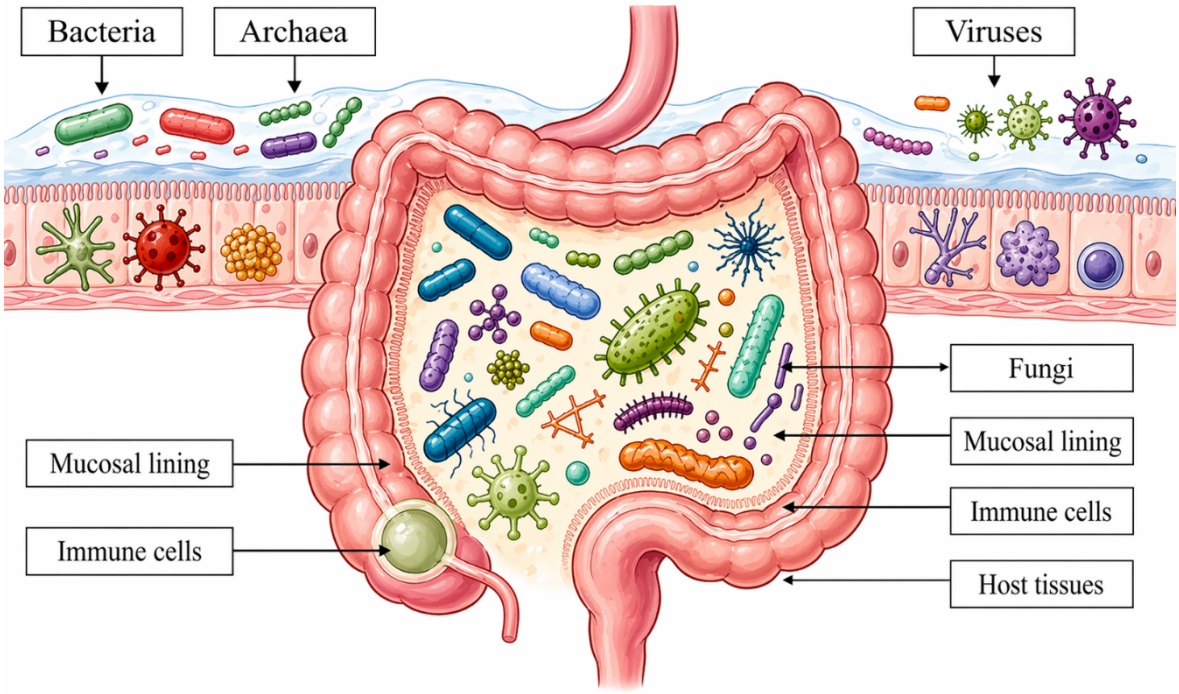


Figure 1. Illustration of the human gut showing key components of the gut microbiota systems biology. Labeled elements include bacteria, archaea, viruses, fungi, immune cells, host tissues, and the mucosal lining, highlighting their interactions and distribution within the gut environment. Image created by the authors using Microsoft Powerpoint.

illustrates the human gut, showing key components of the gut microbiota systems biology.

2. Overview of gut microbiota multi-omics

The rapid evolution of high-throughput sequencing, mass spectrometry (MS), and computational pipelines has transformed microbiome science from descriptive ecological profiling into a comprehensive multi-omics discipline. Multi-omics enables a multi-layered view of the gut microbial ecosystem (Figure 2) spanning microbial genomes, RNA expression, protein activity, metabolite production, and host immune interactions. Integrated analysis across these domains provides a systems-level understanding of microbial function, ecological dependencies, and host–microbe communication.[19]

2.1. Metagenomics and metataxonomics

Metagenomics provides gene- and pathway-level resolution of microbial communities by sequencing total community DNA, enabling taxonomic classification, functional annotation, and strain-level profiling.[20] Shotgun metagenomics surpasses 16S ribosomal RNA amplicon (metataxonomics) sequencing by reconstructing metabolic pathways, antimicrobial resistance genes, virulence factors, and plasmid-encoded functions.[16,21]

Hybrid sequencing approaches that pair Illumina short reads with PacBio/Oxford Nanopore Technologies long reads improve genome assembly quality and microbial pan-genome reconstruction.[22] Recent computational advances, such as reference-free metagenomic assembly, strain-aware binning, and ML–based taxonomic assignment, further enhance the resolution of low-abundance and rare taxa.[23]

Metagenomics has identified microbial networks associated with obesity, diabetes, colorectal cancer, autoimmune disorders, and neuropsychiatric syndromes.[24] However, genome presence does not always equate to functional activity, necessitating complementary functional omics layers.[23]

2.2. Meta-transcriptomics

Meta-transcriptomics profiles community-level RNA, revealing actively expressed genes and capturing context-dependent microbial responses to diet, inflammation, xenobiotics, and pharmaceuticals. RNA sequence-based expression data reflect microbial adaptation to environmental shifts and host immune cues, often diverging from predicted genomic potential.[23]

High-resolution ribosomal RNA depletion and enrichment protocols enable quantification of low-abundance transcripts. Coupled with metabolic modeling, meta-transcriptomics reveals functional microbiota shifts in IBD, colorectal cancer, and metabolic syndrome.

ML models, particularly RNNs and attention-based architectures, have been applied to infer dynamic transcriptional patterns and riboswitch regulation under physiological perturbations.[23]

2.3. Metaproteomics

Metaproteomics quantifies microbial and host proteins, offering direct insight into biochemical activity and microbial–host signaling. MS-based proteomics identifies enzymes driving fermentation, SCFA biosynthesis, xenobiotic metabolism, and immune modulation[25]. Spectral library ML tools (e.g., Prosit) improve the accuracy of peptide identification and quantification[26]. Metaproteomics has elucidated host immune responses, mucosal barrier dynamics, protease activity, and bacterial adhesion pathways in IBD and colorectal cancer[25]. The combined analysis of metagenomics and metaproteomics improves the detection of strain-specific functional pathways and regulatory bottlenecks.[27]

2.4. Metabolomics

Metabolomics characterizes small molecule metabolites, capturing microbial metabolic output and host responses. Advanced liquid chromatography–MS, gas chromatography–MS, and nuclear magnetic resonance platforms enable the identification of SCFAs, bile acids, tryptophan derivatives, fatty acids, neuromodulators, vitamins, and xenobiotics.[28] Microbial metabolites regulate gut–brain signaling, insulin sensitivity, gut epithelial integrity, and regulatory T cell differentiation.[29] Additionally, microbial processes, such as bile acid deconjugation, polyamine metabolism, and indole production, modulate inflammatory pathways relevant to IBD and hepatic steatosis.[30] AI-assisted metabolomics using random forests, autoencoders, and graph models uncovers metabolic signatures predicting cancer risk, metabolic disease onset, and immunotherapy outcomes.[21,27]

2.5. Host–microbiome interaction omics

Host multi-omics reveals molecular responses to microbial signals. Epigenomic analyses (assay for transposase-accessible chromatin sequencing and chromatin immunoprecipitation sequencing) demonstrate microbiota-driven chromatin remodeling in immune cells and the intestinal epithelium.[31] Single-cell transcriptomics maps immune–microbial cross-talk in mucosal and lamina propria compartments.[27] Spatial transcriptomics localizes microbial niches and host cell-state changes

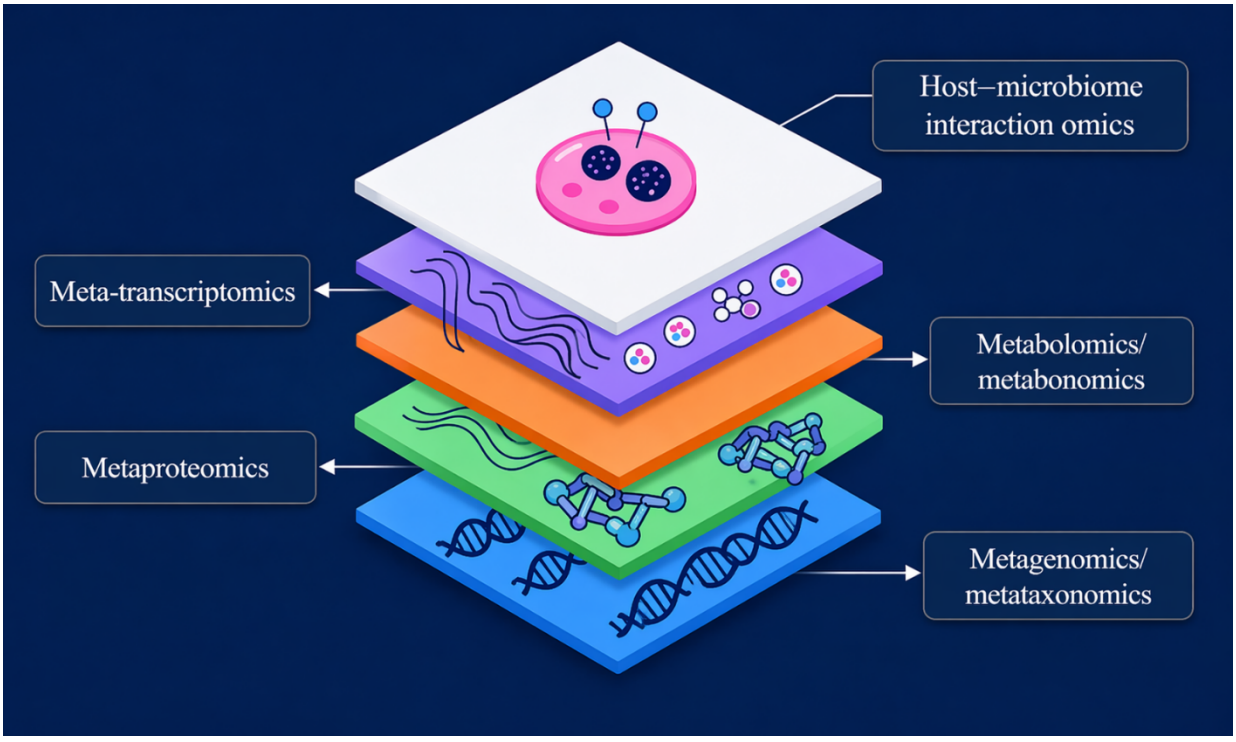


Figure 2. Layered schematic of multi-omics approaches in gut microbiota research, showing metagenomics/metataxonomics at the base, followed by metaproteomics, meta-transcriptomics, metabolomics/metabonomic, and host–microbiome interaction omics (epigenomics and immunomics). Each layer represents a distinct data type and analytical focus within the study of gut microbial ecosystems. Image created by the authors using Microsoft Powerpoint.

in situ, unveiling biofilm-immune microenvironments in IBD and cancer. Integrative modeling of microbial abundances, host gene expression, and metabolite fluxes reveals causal host–microbe circuits and disease-specific immunometabolic axes.[32]

3. Technology ecosystem and computational platforms

3.1. High-throughput sequencing and mass spectrometry-based tools

Modern gut microbiome science is powered by advances in high-throughput sequencing and MS-based metabolite and protein characterization. Illumina sequencing remains the standard for short-read metagenomics due to its accuracy and throughput, while long-read platforms such as PacBio HiFi and Oxford Nanopore Technologies improve strain-level resolution, mobile element detection, and genome assembly continuity.[10] Hybrid sequencing strategies combining short reads and long reads facilitate high-fidelity metagenome-assembled genome reconstruction, particularly from low-abundance taxa.[33] Meta-transcriptomic workflows increasingly incorporate ribosomal RNA depletion and targeted enrichment protocols to enhance detection of microbial regulatory RNA and context-specific transcriptional states. Meanwhile, advances in liquid chromatography–MS, tandem MS/MS, gas chromatography–MS, and nuclear magnetic resonance spectroscopy enable comprehensive metabolite profiling, including SCFAs, bile acids, amino acid derivatives, and neuromodulators.[34] Deep learning-based peptide spectrum prediction (e.g., Prosit) increases metaproteome coverage, improving detection of enzymes, structural proteins, and host immune factors.[35] Together, these platforms constitute the backbone of multi-omics interrogation of gut ecosystems.[36]

3.2. Data integration pipelines and knowledge graphs

Large-scale microbiome studies require standardized workflows and reproducible data integration pipelines. Open-source platforms such as QIIME2, MGnify, Qiita, HUMAnN, and Kraken2/Bracken support taxonomic classification, functional annotation, and harmonization of large sequencing cohorts.[37] Advanced pipelines such as MetaPhlAn4 and HUMAnN3 integrate microbial genomes and pathway databases to infer metabolic potential and activity.[38] Knowledge graphs are increasingly applied to unify multi-omics data, microbial pathways, host interaction maps, and environmental exposures into structured relational graphs.[39] Microbiome knowledge bases, including BugSigDB, MicrobiomeDB, and the Human Microbiome Project (HMP) datasets, support linked-data analysis, hypothesis testing, and meta-analytic inference. Graph-based ML, including GNNs, enables microbial co-abundance network inference, pathway reconstruction, and strain-level host association discovery in large cohorts.[33,36]

3.3. Cloud computing, federated learning, and big data infrastructure

Microbiome studies, mainly longitudinal or population-scale cohorts, generate multi-terabyte multidimensional datasets. Cloud infrastructures (AWS, Google Cloud Platform, Microsoft Azure) provide scalable compute and distributed storage for high-throughput bioinformatics workflows.[40] Containerized pipelines (Docker, Singularity) and workflow engines (Nextflow, Snakemake) support reproducibility and portability across platforms, enabling multi-center analysis.[41] Federated learning frameworks allow decentralized model training without raw data sharing, addressing data privacy restrictions across hospitals and global research networks.[42] FL has shown promise in microbiome-based disease prediction, antimicrobial resistance modeling, and precision nutrition trials, preserving patient privacy while leveraging multi-center datasets. Advances in privacy-preserving computation (differential privacy, secure multiparty computation, and homomorphic encryption) will further enable cross-institutional collaboration and clinical deployment of microbiome AI systems.

3.4. Gut microbiome artificial intelligence platforms and databases

To support AI-driven discovery, specialized computational suites and databases for microbiome analysis have emerged. Tools such as DeepMicro, MicrobiomeAI, MetaPhlAn-Transformer, MMvec, and microbial community modeling combine neural networks with metabolic and ecological modeling.[43] Digital twin builders integrate constraint-based metabolic modeling (COBRA), dynamic flux balance analysis, and deep learning to enable individualized ecosystem simulations and diet/probiotic optimization.[44] Microbiome biobanks and reference atlases, including HMP, GMrepo, gutMGene, and gutMDisorder, provide curated catalogs of microbial species, gene clusters, metabolites, and disease associations.[45] AI-ready benchmarks such as CuratedMetagenomicData and the European Nucleotide Archive enable reproducible benchmarking and cross-cohort validation.[46] These platforms form the computational foundation for next-generation precision microbiome research.

4. Machine learning and artificial intelligence methodologies

4.1. Traditional machine learning algorithms

Traditional ML algorithms have been widely applied in microbiome research due to their robustness and interpretability. Support vector machines excel in binary classification and have been used to distinguish disease from healthy microbial profiles.[47] Random forest models are frequently used to identify key microbial taxa and metabolic features associated with diseases such as IBD, colorectal cancer, and type 2 diabetes by ranking feature importance.[48] The K-nearest neighbors algorithm provides a simple yet effective approach for community classification, particularly in smaller datasets.[49] Gradient boosting models such as XGBoost and LightGBM offer improved predictive accuracy by combining multiple weak learners and performing efficient feature selection, often outperforming traditional regression-based approaches.[50] Although classical models perform well on structured data, they may struggle to capture complex, nonlinear microbial interactions and hidden ecological dependencies without extensive feature engineering.

4.2. Deep learning approaches

Deep learning enables learning directly from raw multi-omics data without extensive preprocessing. Convolutional neural networks capture spatial and phylogenetic relationships in microbial abundance matrices, making them advantageous in disease classification tasks.[51] RNNs and long short-term memory architectures model temporal microbiome dynamics, enabling prediction of microbial shifts during antibiotic treatment, dietary changes, or fecal microbiota transplantation (FMT).[52] Autoencoders and VAEs reduce noise and encode latent biological features, thereby supporting dimensionality reduction and functional-state inference.[53] Recently, transformer-based models, powered by attention mechanisms, have emerged as cutting-edge tools for learning contextual relationships between microbial taxa, genes, and metabolic functions. These models excel in multi-omics fusion and functional gene prediction, outperforming earlier deep learning systems in many microbiome applications.[47,54]

4.3. Graph neural networks for microbial interaction maps

Graph neural networks model microbial ecosystems as interconnected graphs, enabling inference of microbial co-occurrence networks, cross-feeding pathways, and immune–microbial interactions. Unlike traditional models that treat microbial profiles as static feature vectors, GNNs leverage ecological structure, allowing them to identify keystone species, metabolic hubs, and microbial community modules. State-of-the-art implementations such as GraphSAGE, graph attention networks, and knowledge graph frameworks reveal directional microbial influence and metabolic exchange relationships.[55] These methods are particularly effective in uncovering causal ecological mechanisms and predicting functional shifts in response to diet, disease, or therapeutic interventions.[56]

4.4. Reinforcement and active learning for microbiome optimization

Reinforcement learning (RL) offers a dynamic approach to therapeutic optimization, iteratively improving decisions through reward feedback. In the microbiome field, RL has been used to identify optimal personalized diets, probiotic formulations, and microbial consortia that maximize beneficial outcomes such as improved insulin sensitivity or immune modulation.[57] Digital gut twin platforms increasingly incorporate RL to simulate host–microbe interactions and recommend individualized interventions.[58] Active learning complements RL by strategically selecting the most informative microbial samples or experimental conditions, reducing computational costs and experimental effort while accelerating discovery in synthetic microbiology and microbial gene annotation.[59]

4.5. Explainable artificial intelligence and causal modeling

Explainable AI frameworks are essential for translating microbiome AI into clinically actionable tools. Techniques such as Shapley additive explanations, local interpretable model-agnostic explanations, saliency maps, and attention-weight visualization reveal how specific microbial taxa, genes, or metabolites contribute to model decisions, fostering trust and regulatory compliance.[60] Causal inference models go a step further by distinguishing correlation from causation, allowing researchers to identify microbes and pathways that drive disease rather than merely associate with it.[61] Bayesian networks and structural causal models uncover directional host–microbe influences, supporting the rational design of probiotics, targeted antimicrobials, and dietary strategies.[62] Together, explainable AI and causal modeling enhance interpretability, reproducibility, and mechanistic insight in microbiome AI pipelines.[63,64]

5. Multi-omics data integration frameworks

Understanding gut microbiome function requires harmonizing diverse layers of biological information, including microbial genomes, transcripts, proteins, metabolites, dietary inputs, and host immune responses. Multi-omics integration frameworks enable the mapping

Table 1. Overview of artificial intelligence and machine learning workflow in microbiome research

Step	Description	Key techniques/tools	References
Data collection	Acquire microbiome and clinical datasets	16S ribosomal RNA, metagenomics, metabolomics, the Human Microbiome Project, National Center for Biotechnology Information, European Nucleotide Archive	65
Data preprocessing	Clean, normalize, and prepare data	Quality filtering, log-ratio transformation, dimensionality reduction (principal component analysis, autoencoders)	66
Feature engineering	Extract relevant features for modeling	Operational taxonomic units, species abundance, functional pathways	47
Machine learning modeling	Train predictive or descriptive models	Random forest, support vector machine, gradient boosting, convolutional neural network, recurrent neural network	67
Model validation	Evaluate model performance	Cross-validation, receiver operating characteristic curves, and external validation cohorts	68
Interpretation	Explain model predictions	Shapley additive explanations, feature importance ranking	69
Ethical considerations	Ensure responsible artificial intelligence use	Privacy, bias, reproducibility, transparent reporting	70

of microbial activity states, ecological interactions, and host signaling pathways with unprecedented resolution. Modern computational strategies combine network biology, latent-space representations, probabilistic modeling, and digital twin simulations to decode the molecular architecture of host–microbiome systems and predict therapeutic outcomes.[71]

5.1. Network-based and multi-layer graph models

Network-based multi-omics integration uses graph theory to represent biological interactions across molecular layers. Multi-layer interaction networks combine taxonomy, gene co-expression, protein–protein interactions, metabolic exchange, and immune signaling into a unified graph.[72] These approaches map microbial ecological interactions, infer cross-feeding and metabolic competition, identify keystone species and functional hubs, and reveal host–microbe regulatory cascades.

Techniques such as multi-layer GNNs, co-abundance networks, metabolic flux networks, and knowledge graphs allow mechanistic modeling of microbiome structure and dynamics. This enables identification of microbe–metabolite modules linked to inflammation, metabolic disease, and neuroimmune pathways, offering biologically grounded prioritization of therapeutic targets.[73]

5.2. Multi-modal feature fusion strategies

Multi-modal fusion integrates heterogeneous omics signals into a unified predictive model. Early-integration methods concatenate raw features across omics layers (e.g., taxa, transcripts, and metabolites), while intermediate fusion methods learn shared representations using attention mechanisms or latent-space encoders. Late-integration models combine outputs of modality-specific models and aggregate decision layers.[74] Modern architectures, including transformers, contrastive learning models, and cross-modal autoencoders, outperform traditional pipelines by learning relationships between omics layers rather than treating them independently. These frameworks excel in tasks such as disease classification, diet response profiling, and immunotherapy prediction, where integrating microbial and host biomarkers is essential.[75]

5.3. Bayesian learning and probabilistic inference

Bayesian models provide principled frameworks for uncertainty quantification, causal reasoning, and domain adaptation in microbiome analytics. Probabilistic graphical models capture dependencies among host metabolites, microbial taxa, immune signatures, and environmental exposures.[76] Hierarchical Bayesian models account for heterogeneity across populations, sequencing platforms, and diet regimes, improving generalizability.[77] Bayesian network inference supports causal hypothesis testing, distinguishing microbial features that merely correlate with disease from those that actively modulate physiological pathways.[78] These frameworks also enable uncertainty-aware clinical decision support, increasing confidence in AI-guided precision interventions.[79]

5.4. Latent space alignment and dimensionality reduction

Dimensionality reduction is essential for simplifying high-dimensional multi-omics datasets. Algorithms such as principal component analysis, non-negative matrix factorization, and uniform manifold approximation and projection extract meaningful low-dimensional

structure.[80] Deep learning models like autoencoders, VAEs, and diffusion models learn multi-omics latent spaces that disentangle biological signals from noise.[81]

Latent-space alignment techniques match microbial gene functions to metabolite outputs, immune states, and clinical phenotypes.[82] These compact biological embeddings allow the discovery of latent health signatures, dietary response modules, and microbial functional guilds associated with metabolic or neuroimmune phenotypes.[83,84]

5.5. Digital twin and microbiome simulation models

Digital twin models integrate mechanistic metabolic networks, agent-based simulations, and deep learning to create personalized computational replicas of the gut ecosystem. These models simulate diet–microbe–immune interactions and predict responses to probiotics, prebiotics, FMT, antibiotics, or precision nutritional strategies.[85] Mechanistic backbones (e.g., COBRA, microbial community modeling, dynamic flux balance analysis) are combined with neural networks to capture emergent ecosystem behavior and host physiology.[86] Digital twin frameworks represent a transformative direction in precision medicine, allowing *in silico* intervention testing and optimization before real-world treatment, thereby accelerating personalized microbiome therapeutics.[87]

6. Applications in health and disease

The integration of multi-omics and AI has accelerated the understanding of how the gut microbiota influences diverse physiological systems and disease states. ML-derived microbial signatures now support the detection of early disease, the prediction of therapy response, and the design of precision interventions. AI frameworks also facilitate the discovery of next-generation probiotics, inform FMT protocols, and enable personalized dietary recommendations by linking microbial metabolism to host phenotypes. Together, these advances are reshaping diagnostic frameworks and therapeutic paradigms in modern medicine.[88]

6.1. Gut microbiome signatures in major diseases

6.1.1. Metabolic disorders

Dysbiosis in metabolic disease is characterized by reduced microbial diversity, loss of butyrate-producing taxa, and enrichment of pathobionts with pro-inflammatory metabolic profiles.[89] AI has identified microbial signatures predicting insulin resistance, obesity progression, and glycemic responses to diet.[90] SCFA producers, such as *Faecalibacterium prausnitzii* and *Akkermansia muciniphila*, demonstrate protective associations, while branched-chain amino acid-producing microbes correlate with metabolic inflammation.[91] Transformer-based models now integrate metagenomics, metabolomics, and dietary logs to forecast glycemic indices and predict response to lifestyle interventions.[58]

6.1.2. Cancer and immunotherapy response prediction

The gut microbiome modulates anti-tumor immunity through metabolite-driven immune activation and modulation of checkpoint pathways. Specific taxa—including *Bifidobacterium*, *Akkermansia*, and *Ruminococcus*—enhance responses to anti-programmed death-1 and anti-cytotoxic T lymphocyte-associated antigen 4 therapies.[92] Deep learning models predict patient immunotherapy outcomes based on microbial composition and metabolomic signatures, outperforming standard clinical markers.[93] Multi-omics-informed digital twins simulate tumor–immune–microbiome interactions to optimize combination immunotherapies and probiotic co-adjuvant strategies.[45]

6.1.3. Neuro–gut axis and neurodegenerative diseases

Microbial metabolites, such as tryptophan derivatives, bile acids, and SCFAs, interact with the vagus nerve, microglia, and neuroendocrine circuits to shape neurological development and behavior.[94] AI has uncovered microbiome alterations associated with Parkinson's disease, Alzheimer's disease, autism, and major depression.[95] Psychobiotic therapy pipelines now use ML-derived microbial signatures to identify mood-modulating strains and predict cognitive or behavioral outcomes based on gut metabolome profiles.[96]

6.1.4. Gastrointestinal diseases

Inflammatory bowel disease is characterized by reduced microbial diversity, expansion of facultative anaerobes, mucosal dysbiosis, and altered SCFA pathways. ML classifiers identify microbial markers of IBD severity and post-treatment outcomes, while spatial-omics models map microbe-mucosa interactions.[97] In IBS, ML models delineate strain-specific metabolic differences associated with dietary triggers, gut motility phenotypes, and visceral hypersensitivity.[47]

6.1.5. Infection, antibiotics, and resistance

Artificial intelligence supports the prediction of antibiotic resistance gene dissemination, the identification of microbial drivers of *Clostridioides difficile* infection, and the modeling of microbiome–antibiotic recovery trajectories.[98] Multi-omics signatures guide rational microbial restoration strategies to mitigate infection and antimicrobial resistance development, including symbiotic and bacteriophage therapies.[98]

6.2. Precision probiotics and next-generation psychobiotics

Artificial intelligence accelerates probiotic discovery by screening microbial genomes, metabolic outputs, and ecological interaction profiles. Next-generation probiotics such as *Akkermansia*, *Christensenella*, and engineered *Bacteroides* strains target barrier repair, SCFA biosynthesis, bile acid modulation, and neuromodulator synthesis.[99] Psychobiotics, designed to regulate stress pathways, neurotransmitter metabolism, and inflammation, are being prioritized using deep learning models that link specific strains to neurotransmitter precursors and brain–immune modulators.[100]

6.3. Fecal microbiome transplantation optimization

Fecal microbiome transplantation outcomes vary widely across patients. AI models predict donor–recipient compatibility, identify "super donors," and forecast treatment success in recurrent *C. difficile* infection, ulcerative colitis, and cancer immunotherapy.[101] Multi-omics-guided FMT optimization focuses on strain engraftment profiles, metabolite dynamics, and immune activation signatures.[102] RL-based models are emerging to refine dosing, route, and donor matching parameters.[42]

6.4. Nutritional artificial intelligence and personalized diet microbiome models

Diet profoundly influences microbial structure and function. AI-driven personalized nutrition systems integrate microbiome profiles, metabolomics, and continuous glucose monitoring to craft individualized dietary strategies.[103] Models predict glycemic responses, lipid modulation, and inflammatory potential of foods, enabling highly tailored precision diet recommendations.[104] Diet–microbiome digital twins simulate metabolic consequences of fiber, polyphenol, and prebiotic interventions to steer long-term health trajectories.[104] Table 2 represents the applications of ML and AI in multi-omics-based gut microbiota research.

6.5. Microbial biomarker discovery

Multi-omics combined with ML has enabled robust biomarker discovery for disease detection, progression monitoring, and therapy response prediction. Biomarkers include microbial taxa, strain-specific gene modules, metabolite signatures (e.g., secondary bile acids, SCFAs), and microbial–immune interaction scores. Explainable AI ensures model interpretability, linking computational outputs to mechanistic biology and regulatory standards

Table 2. Applications of machine learning and artificial intelligence in multi-omics–based gut microbiota research

AI/ML approach	Multi-omics data type	Primary functions in gut microbiota research	Key outcomes/advantages
Classical ML	Metagenomics, metabolomics	Feature selection, microbial biomarker identification, disease classification	High predictive accuracy; robust handling of heterogeneous datasets [106]
Deep learning	Metagenomics, meta-transcriptomics	Pattern recognition, sequence analysis, functional gene prediction	Captures nonlinear relationships; scalable to large datasets[107]
Graph neural networks	Microbial interaction networks, host–pathogen networks	Ecological interaction mapping, network modeling	Reveals hidden microbe–microbe and microbe–host communication pathways[108]
Multi-modal data fusion models	Meta-omics integration (DNA, RNA, proteins, metabolites)	Integrating diverse omics layers into unified models	Holistic view of functional microbiome states[109]
Explainable AI	All omics layers	Model interpretability, explanation of microbial contributions	Transparent decision-making; biomarker validation[110]
Reinforcement learning	Diet–microbiome interaction datasets, therapeutic simulations	Optimizing personalized interventions, dietary recommendations	Enables adaptive and personalized therapeutic strategies[111]
Bayesian and causal inference models	Host immune and metabolic omics, microbiome profiles	Causal relationship detection, mechanism discovery	Predicts mechanistic drivers rather than correlations[78]
Digital gut twins	Integrated multi-omics + clinical datasets	Simulation of host–microbe interactions and treatment responses	Personalized predictions for nutrition, probiotics, and therapeutics[112]
AI-guided microbial engineering tools	Genomics, CRISPR editing datasets	Predicting gene targets, strain optimization	Accelerates design of next-generation probiotics and symbiotics[113]

(*Cont'd...*)

Table 2. *(Continued)*

AI/ML approach	Multi-omics data type	Primary functions in gut microbiota research	Key outcomes/advantages
AI-assisted microbiome drug discovery	Metabolomics, metaproteomics	Identifying microbiome-derived metabolites and therapeutic peptides	Faster discovery pipelines; high-throughput screening capabilities[114]
Single-cell AI models	Single-cell metagenomics and transcriptomics	Resolving cellular heterogeneity, rare taxa detection	Unprecedented resolution of microbe–host interactions[115]
Organoid–AI platforms	Host epithelial, immune omics + microbial signals	Predicting host responses in controlled environments	Enhanced translational accuracy for clinical applications[116]

Abbreviations: AI: Artificial intelligence; CRISPR: Clustered regularly interspaced short palindromic repeats; ML: Machine learning.

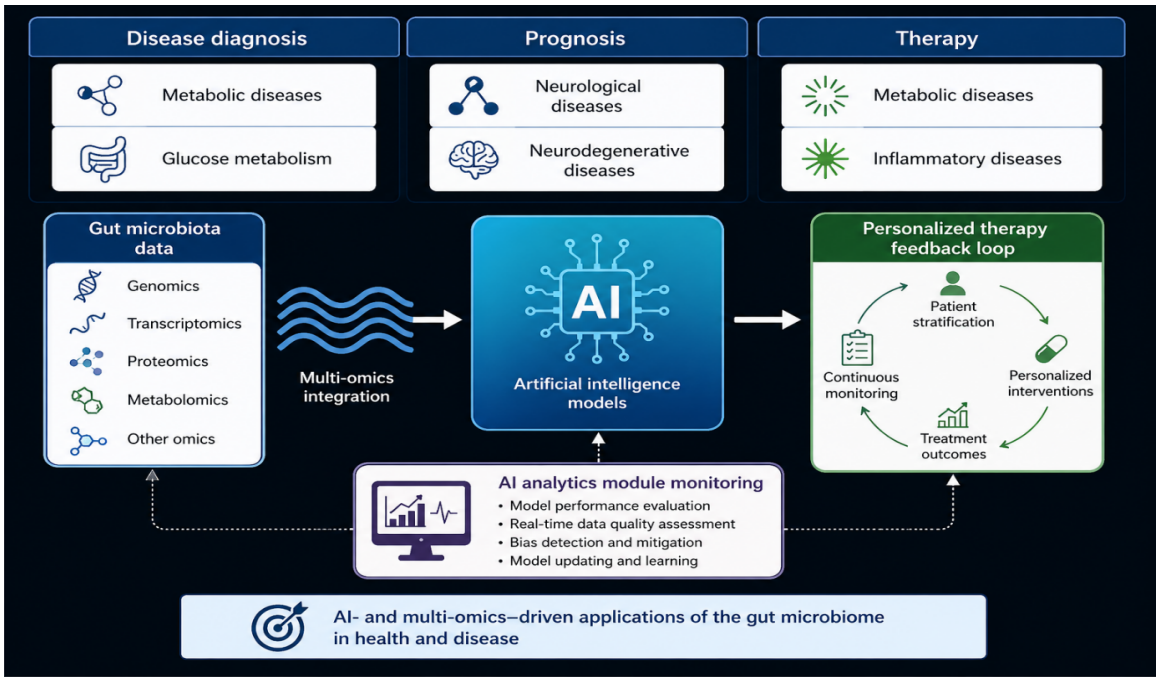


Figure 3. The integration of gut microbiome-derived multi-omics data with artificial intelligence (AI) approaches for disease diagnosis, prognosis, and therapeutic decision-making. The figure highlights how AI-based analytical frameworks enable precision medicine and personalized healthcare. Image created by the authors using Microsoft Powerpoint.

for clinical diagnostics.[105] Figure 3 illustrates the integrative multi-omic data of the gut microbiome using AI.

7. Emerging opportunities and challenges

The convergence of AI, synthetic biology, and next-generation experimental systems is transforming microbiome research from observational analysis to rational design and predictive intervention. These advances enable targeted control of microbial communities, mechanistic dissection of host–microbe interactions, and development of precision therapeutics tailored to individual microbiome states. AI-powered pipelines and engineered platforms are unlocking a new era of programmable microbiome medicine.[117]

7.1. Artificial intelligence-enabled drug discovery and microbiome-based therapeutics

Artificial intelligence is accelerating the discovery of microbiome-modulating drugs, including postbiotics, small molecule inhibitors, bacteriophages, engineered probiotics, and microbiome-derived metabolites.[118] ML frameworks screen microbial metabolites for immunomodulatory effects, predict bioactive peptides, and identify microbial enzymes influencing host inflammation, neurotransmission, and metabolism.[119] Deep generative models and RL guide *de novo* design of small molecules targeting microbial metabolic pathways, virulence factors, and quorum-sensing networks.[120] Multi-omics biomarkers increasingly support the precision

deployment of microbiome-adjuvant therapies in cancer immunotherapy, metabolic disorders, and neuropsychiatric disease.[121] Together, these approaches advance AI-assisted microbiome pharmacology as a core pillar of translational medicine.[122]

7.2. Clustered regularly interspaced short palindromic repeats-enabled microbiome editing and synthetic biology

Clustered regularly interspaced short palindromic repeats–Cas tools enable precise editing of gut microbes to modulate gene expression, metabolic pathways, and virulence factors. Engineered probiotic platforms are being developed to deliver therapeutic peptides, remove toxic metabolites, and suppress pathogens through sequence-specific gene targeting.[123] Synthetic biology approaches allow the design of programmable microbial consortia, chassis strains, and microbial circuits responsive to host immune or dietary cues.[124] AI models assist metabolic circuit design, predict off-target gene interactions, and optimize strain stability. This convergence supports next-generation "living biotherapies" capable of delivering targeted, long-term therapeutic effects.[125]

7.3. Gut-on-chip and organoid–artificial intelligence integration

Microfluidic gut-on-chip systems and intestinal organoids recreate physiologically relevant microenvironments, enabling precise investigation of host–microbe interactions. AI enhances these platforms by analyzing real-time imaging, multi-omics outputs, and microfluidic response signatures to identify microbial impact on barrier integrity, immune signaling, and neuromodulation.[126] Organoid co-culture models simulate mucus gradients, peristaltic motion, and immune cell infiltration, providing mechanistic insight into probiotic actions, pathogen colonization, and drug–microbiome interactions.[127] Integration of organoid models with predictive AI accelerates preclinical microbiome therapeutic testing and supports personalized *ex vivo* intervention screening.[128]

7.4. Single-cell microbiomics and artificial intelligence

Single-cell microbial genomics, transcriptomics, and epigenomics enable unprecedented resolution of microbial heterogeneity and host–microbial interactions. AI enhances cell-state mapping, lineage tracing, contaminant removal, and rare-cell detection across complex microbial communities.[129] Single-cell multi-omics reveals strain-specific metabolic pathways, antibiotic resistance niches, and immune-interacting phenotypes within the gut.[130] Combined with spatial transcriptomics and immune profiling, AI-integrated single-cell microbiomics uncovers micro-biogeography, revealing microbe–host interactions within mucosal niches of IBD, cancer, and infection.[131]

7.5. Human digital twin microbiome ecosystems

Digital twin platforms create computational replicas of the human gut ecosystem that simulate microbial ecology, immune dynamics, diet responses, and therapeutic interventions. These models integrate agent-based simulations, metabolic flux modeling, and neural networks to predict microbiome responses to drugs, dietary fiber, prebiotics, and engineered probiotics. Digital gut twins support *in silico* clinical trials, donor–recipient FMT matching, and RL-guided personalized nutrition.[132] As models incorporate immunomics, neuroendocrine pathways, and host genetics, they will serve as predictive engines for precision microbiome medicine and adaptive therapy optimization.

7.6. Challenges

Despite rapid advances at the intersection of AI and microbiome science, significant challenges remain across data generation, computational modeling, and real-world translation. Overcoming these limitations requires coordinated progress in standardization, ethics, regulatory compliance, and population-level diversity. Addressing these obstacles will be critical to ensure equitable, safe, and scientifically rigorous deployment of AI-enabled microbiome medicine.[133]

7.6.1. Multi-omics data standardization

Standardizing multi-omics of the microbiome remains a foundational barrier. Variability arises from sample collection methods, DNA/RNA extraction protocols, sequencing platforms, library preparation, computational pipelines, and taxonomic classifiers.[134] Batch effects, compositional bias, incomplete reference databases, and inconsistent metadata frameworks further complicate cross-study harmonization. While efforts such as the HMP, Earth Microbiome Project, and Findable–Accessible–Interoperable–Reusable principles promote harmonization, continuous benchmarking, ontology alignment, and interoperable data formats remain essential for reproducible multi-omics integration.[135]

7.6.2. Data privacy, bias, and reproducibility

Large-scale microbiome data collection raises privacy concerns due to potential re-identification risks from genomic and lifestyle-linked metadata. Bias can arise from unbalanced cohort representation, geographic skew, and incomplete clinical metadata, leading to models that generalize poorly across populations or clinical

settings.[136] Reproducibility remains constrained by limited accessibility to raw datasets, inconsistent preprocessing, and proprietary computational pipelines. Federated learning, standardized benchmarking datasets, and transparent algorithm reporting frameworks are emerging solutions, yet scalable implementation requires wider institutional and regulatory support.[45]

7.6.3. Model interpretability and clinical translation

Artificial intelligence-derived insights must be mechanistically interpretable to gain clinician and regulatory trust. Deep models often act as "black boxes," limiting clinical adoption despite high predictive accuracy.[137] Explainable AI techniques, causal inference, and hybrid mechanistic-statistical models are critical to connecting computational predictions to biological plausibility. Furthermore, clinical integration requires prospective validation, assay standardization, diagnostic scoring frameworks, and demonstration of economic and therapeutic benefit. Transitioning from correlation-based discoveries to mechanistic causal biomarkers remains a central challenge.[14]

7.6.4. Regulatory, ethical, and security considerations

Regulatory frameworks for microbiome–AI systems are still evolving. Ethical concerns include algorithmic bias, patient consent for multi-omics data aggregation, and governance for AI-generated therapeutic recommendations.[138] Microbiome manipulation—via engineered probiotics, phages, and clustered regularly interspaced short palindromic repeats-modified microbes—raises biosafety and dual-use biosecurity concerns. Regulatory agencies such as the Food and Drug Administration and European Medicines Agency are developing digital health and live-biotherapeutic guidelines, yet a unified global framework for microbiome–AI oversight, model auditing, and real-time safety monitoring is still needed.[19,139]

7.6.5. Integration of cultural, dietary, and population diversity

Microbiome composition varies significantly across cultures, geographies, ethnicities, and dietary traditions. Many microbiome–AI models are trained on Western or urban cohorts, limiting generalizability in global populations. Indigenous diets, fermented food traditions, and rural/migrant microbiomes remain underrepresented. Equitable microbiome science requires inclusion of diverse cohorts, culturally informed dietary research, and global biobank networks to avoid widening disparities in precision medicine. AI frameworks must account for socio-cultural determinants, nutritional habits, and environmental exposures to deliver context-appropriate recommendations.[140]

8. Future roadmap

The convergence of advanced AI, multi-omics platforms, and mechanistic microbiology will drive the future of microbiome science. This shift marks a transition from association-based studies to predictive, intervention-oriented frameworks capable of modeling causal interactions and designing targeted microbial modulation strategies. As the field evolves, integrating large-scale datasets, standardized metadata pipelines, digital health streams, and computational biology will unlock truly personalized, real-time microbiome medicine. The long-term vision is to create deeply integrated biological intelligence systems capable of continuously interpreting host physiology, microbial function, environmental exposure, and lifestyle behavior to generate dynamic health-optimizing interventions. This evolution will blur the line between diagnostics, therapeutics, and preventive medicine, positioning the microbiome at the center of next-generation precision health ecosystems.

8.1. Artificial intelligence-first microbiome research paradigm

Microbiome science is rapidly shifting toward an AI-first paradigm in which computational models do not merely analyze experiments but actively shape research strategy. Instead of hypothesis-driven data collection, AI systems assist in hypothesis generation, experimental prioritization, and causal modeling before wet lab execution. Foundation models trained on multi-omics and clinical data learn microbial "language," biological grammar, metabolic logic, and immunological signaling rules, enabling them to predict microbial interactions, emergent community states, and therapeutic leverage points.[141] AI-driven simulation guides strain selection, synthetic consortium design, and dietary intervention architecture before empirical testing.[54,142] Continuous learning systems update models with new sequencing runs, clinical results, wearable data, metabolomic shifts, and environmental inputs.[143] This AI-native research pipeline can dramatically accelerate discovery cycles, reduce experimental cost, and enable autonomous inference of microbiome–host rules, fundamentally transforming scientific methodology in the life sciences.[144]

8.2. Findable–Accessible–Interoperable–Reusable multi-omics frameworks

As multi-omics datasets scale across continents, data interoperability and Findable–Accessible–Interoperable–

Reusable principles will be essential to ensure reproducibility and equitable access. Future microbiome research ecosystems will require globally harmonized metadata standards, shared reference genomes, and unified pipelines for metagenomics, meta-transcriptomics, metabolomics, proteomics, and immunomics.[10,145] Cloud-native infrastructure and federated learning nodes will enable secure, multi-institutional model training without centralized data pooling, preserving privacy while amplifying statistical power. Automated clinical metadata captured from electronic health records, wearable biosensors, digital diet logs, and lifestyle tracking tools will ensure contextual accuracy. The creation of globally coordinated microbiome biobanks, benchmarking consortia, and ethically governed data trusts will empower scalable translational research while preventing algorithmic bias and regional inequities. This will enable a unified, global computational "language" for microbiome science.[32,63]

8.3. Toward clinically validated artificial intelligence–microbiome biomarkers

The next frontier in clinical microbiome research is the establishment of AI-validated, mechanistically supported microbial biomarkers that meet regulatory standards comparable to those for genomic diagnostics. These biomarkers will require prospective validation across multi-ethnic cohorts, mechanistic causal support through experimental models, and standardized measurement assays such as quantitative polymerase chain reaction-based microbial panels, liquid chromatography–MS metabolomics, or metagenomic signatures. Future diagnostic frameworks will integrate multi-omics microbial features with host immune signatures, inflammatory markers, neural–endocrine indicators, and environmental stress profiles. Clinical decision-support systems will embed microbiome biomarkers within precision care workflows, identifying patients most likely to benefit from immunotherapy, predicting metabolic trajectories, or stratifying neuropsychiatric disease subtypes based on gut–brain signatures. Regulatory agencies will increasingly require explainability, real-world evidence, and long-term performance surveillance, ensuring that microbiome–AI technologies are trustworthy, robust, and actionable in diverse clinical environments.[146,147]

8.4. Precision nutrition, microbiome multi-omics, and lifestyle artificial intelligence

The microbiome sits at the intersection of diet, behavior, and physiology, making precision lifestyle medicine a natural extension of microbiome research. AI-powered nutritional platforms will integrate metagenomic and metabolomic profiles with continuous glucose monitors, digital food logs, sleep patterns, physical activity, and circadian rhythm biomarkers.[32] These systems will generate adaptive dietary strategies to optimize metabolic health, immune balance, and mental well-being by modulating microbial pathways instead of simply delivering macronutrient targets. Pharmaco-microbiomics will predict how microbial enzymes modify drug bioavailability, toxicity, and efficacy, informing drug dosing, identifying microbial biomarkers of therapeutic response, and guiding co-administration of probiotics or dietary elements to maximize therapeutic benefit. Over time, these systems will evolve into daily life companions that continuously tune microbial–host interactions via nutrition, sleep optimization, stress modulation, and microbiome-aware behavioral interventions.[148]

8.5. Grand vision: Gut–brain–immune metaverse

The long-term trajectory of microbiome science points toward the creation of a gut–brain–immune digital metaverse, a real-time computational layer simulating molecular, microbial, and neural–immune interactions within each individual.[59] In this paradigm, multi-omics biosensing, wearable neurophysiological data, immune phenotyping, and continuous digital health inputs feed into personal digital twins that predict physiological shifts and proactively recommend microbial interventions. These systems will simulate microbe-driven emotional regulation, stress resilience frameworks, cognitive performance modulation, and neuroinflammation control.[149] Microbiome-driven neuromodulation through postbiotics, Psychobiotics, neurometabolites, and engineered microbial neurotransmitter circuits may eventually support mood stabilization, memory enhancement, and neuroprotection. This integrated digital–biological ecosystem signals a future in which microbiome interventions become central to emotional health, cognitive longevity, and human resilience, transforming medicine from reactive disease treatment into proactive human optimization.

9. Conclusion

The integration of multi-omics technologies with AI and ML has opened new frontiers in microbiome research, enabling unprecedented insights into complex host–microbe interactions. These computational approaches allow researchers to analyze high-dimensional datasets from genomics, transcriptomics, proteomics, metabolomics, and clinical metadata in a systematic and scalable manner. By applying supervised and unsupervised ML algorithms and deep learning techniques, it is possible to identify predictive microbial signatures, uncover latent relationships, and generate hypotheses about the

mechanisms underlying human health and disease. Despite these advancements, several challenges persist. Microbiome datasets are inherently heterogeneous, compositional, and longitudinal, which requires careful preprocessing, normalization, and feature engineering. Model interpretability remains a critical issue, as black box AI models can obscure the biological significance of predictive patterns. Ethical and regulatory considerations, including data privacy, informed consent, algorithmic bias, and reproducibility, must be rigorously addressed to ensure responsible application in clinical and translational research. Furthermore, standardized reporting guidelines and open-source data sharing are essential to enhance transparency and comparability across studies. Future research should focus on combining multi-omics integration with advanced AI/ML frameworks to improve predictive accuracy and biological interpretability. Collaborative efforts across computational, clinical, and experimental domains will be vital to translate AI-driven insights into actionable outcomes, such as personalized interventions, diagnostics, and therapeutic strategies. Overall, the convergence of multi-omics and AI/ML represents a transformative paradigm for precision microbiome medicine, with the potential to significantly advance our understanding of microbial contributions to health and disease while addressing current methodological and ethical challenges.

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