

The Human Microbiome in Healthcare: Ecological Mechanisms, Disease Associations and Evidence-Based Clinical Translation

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ABSTRACT

Background: The term microbiota refers to the microorganisms that colonize a particular body site, whereas microbiome is generally used for their collective genomes, functional capacity and ecological context. Bacteria are the best-characterized members of these communities, but archaea, fungi, bacteriophages and other viruses also shape community behavior. **The purpose:** Microorganisms live in the human body and impact the ecology of the mucous membranes, host metabolism, and immune regulation; however, the clinical relevance of the variation of the human microbiome varies greatly among diseases. This review critically analyzes the oral and intestinal microbiome biology, clinical links, measurement challenges and therapeutic evidence. **Methods:** The foundational studies, mechanistic studies, randomized trials, regulatory documents, or practice guidelines were purposively selected up to October 2026 for a critical narrative review. **Findings:** Oral and intestinal microbial communities are site-specific, functionally diverse, and their composition is changed by inflammation, antibiotics, diet, and other exposures to the host, making causal interpretation difficult. Microbial associations have been consistently found in both periodontitis and inflammatory bowel disease, but for the individual, microbiome testing is not frequently used to guide treatment. Strain resolved analyses indicate that specific *Fusobacterium nucleatum* strains are involved in colorectal cancer pathogenesis, but there is no routine clinical use. There is a well-defined indication for using microbiota-based interventions in adults for the prevention of recurrent *C. difficile* infection in cases where the patients are appropriately selected, and it is still investigational in other gastrointestinal disorders. **Implications:** Clinical translation requires prospective validation, reproducible multi-omics measurement, transparent reporting, clinically meaningful outcomes and careful assessment of infectious risk. Microbial associations should not be presented as evidence that modifying the microbiome will improve disease outcomes.

Keywords: Human Microbiome, Oral Microbiota, Gut Microbiota, Dysbiosis, Host–Microbe Interactions, Periodontal Disease, Colorectal Cancer, *Clostridioides Difficile*, Microbiota Therapeutics, Precision Medicine.

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INTRODUCTION

The term microbiota refers to the microorganisms that colonize a particular body site, whereas microbiome is generally used for their collective genomes, functional capacity and ecological context. Bacteria are the best-characterized members of these communities, but archaea, fungi, bacteriophages and other

viruses also shape community behavior. Over the past two decades the field has moved from cataloguing taxa toward asking what these organisms actually do, how they interact with one another and with the host, and whether changing a community improves patient outcomes (Human Microbiome Project

Consortium, 2012; Lynch & Pedersen, 2016; Sender et al., 2016). Some long-repeated assumptions have not survived this scrutiny. The claim that microbial cells outnumber human cells by ten to one, for example, is not supported by current estimates, which place the ratio of bacterial to human cells closer to one to one (Sender et al., 2016).

Oral and intestinal niches differ in oxygen tension, nutrient supply, epithelial structure and immune pressure, so they cannot be treated as interchangeable microbial reservoirs. Even within a single organ, saliva, tooth surfaces, gingival pockets, mucosal biopsies and fecal specimens may provide different ecological information. In the same way, dysbiosis describes a community that differs from a chosen comparator; it is not a universally validated clinical diagnosis. For healthcare, the central problem is to separate microbial signatures that are consequences of illness from those that contribute causally to disease or that predict treatment response with useful accuracy (Human Microbiome Project Consortium, 2012; Knight et al., 2018; Lynch & Pedersen, 2016).

This review has four aims: (i) to explain the core ecological mechanisms of the oral and gut microbiota; (ii) to evaluate the evidence for selected diseases; (iii) to distinguish clinically supported microbiota-directed therapies from research applications; and (iv) to identify methodological priorities. The core topics are the oral microbiota, periodontal pathology, the structure of the gut community, the factors that alter the gut microbiota and intestinal immune relationships. These topics are extended here to cover clinical trial evidence, the limitations of sequencing, microbial therapeutics and barriers to implementation.

METHODS

This article is a critical narrative review and not a systematic review or meta-analysis. A targeted review of seminal studies of the microbiome was done, along with an

examination of the literature regarding reporting standards for microbiome research, mechanistic studies for diseases, the 2024 American Gastroenterological Association (AGA) guideline, U.S. Food and Drug Administration (FDA) product documentation, and selected recent investigations. The method was not exhaustive and deliberate. The manuscript should not be interpreted as an evidence map since no reproducible database search string, prospective protocol, dual screening or formal risk-of-bias assessment or pooled effect estimate was performed. The recommendations provided in this review are those of the source guideline; no recommendations are made in this review.

RESULTS

Ecological Organization of the Human Microbiome

Oral Microhabitats

There are adjacent but separate microbial habitats in the mouth, such as the saliva, the dorsum of the tongue, the buccal mucosa, enamel surfaces, subgingival plaque and the gingival crevice. The organisms found in each habitat will depend on the salivary proteins, pH, oxygen level, host-derived nutrients, tooth eruption, diet of carbohydrates and the frequency of mechanical disruption. Common genera found include: *Streptococcus*, *Veillonella*, *Prevotella* and *Actinomyces*, in addition to a number of different anaerobes, relative abundance can be highly variable between individuals and sampling sites (Kilian et al., 2016). Coaggregation and interspecies signaling aid in the development of multilayered biofilms that limit the effect of a sudden change in environmental conditions and that can enhance the tolerance of bacteria to antimicrobials.

Early in life the oral communities begin to develop and alter significantly after the teeth come through. They can also be modified by oral hygiene practices, tobacco exposure,

periodontal inflammation, diabetes and salivary hypofunction. Saliva is convenient to collect, but it is not a direct substitute for subgingival sampling when periodontal communities are being evaluated. A list of taxa presented without spatial and functional context can also conceal organisms that become pathogenic only within particular ecosystems (Kilian et al., 2016).

Gastrointestinal Gradients

Microbial density generally rises from the stomach and proximal small intestine toward the colon, following gradients in acidity, transit time, oxygen tension, bile acid concentration and substrate availability. The colon supports dense anaerobic consortia that metabolize dietary fibers and host-derived glycans. Communities in the intestinal lumen, in the mucus layer and on the mucosal surface are not identical. Stool therefore represents many colonic organisms reasonably well as a noninvasive sample, but it does not adequately characterize the upper gastrointestinal tract or the tissue-adherent microbiota (Human Microbiome Project Consortium, 2012; Lynch & Pedersen, 2016).

In infancy, the developing microbiota is shaped by mode of delivery, gestational age, feeding practice, antibiotic exposure and environmental contact. Adult communities may resist short-term perturbation, yet they shift with sustained dietary change, antimicrobial courses, infection, travel, disease activity and medication use. A universal definition of a healthy microbiome cannot currently be defended, and the functional resilience of a community may matter as much as its taxonomic composition (Human Microbiome Project Consortium, 2012; Lynch & Pedersen, 2016).

Beyond Bacteria

The mycobiome, archaeome and virome are further interacting components of the microbiome. Bacteriophages help shape the ecology and ecology of horizontal gene transfer

of bacteria, and fungi and archaea participate in interkingdom competition and metabolism. The role of these components in clinical significance is not fully understood, partly due to the fact that most studies rely on 16S-based surveys which lack adequate measures of these components. Dedicated assays, appropriate extraction protocols and orthogonal functional studies are needed before cross-kingdom associations are given a clinical interpretation (Knight et al., 2018; Lynch & Pedersen, 2016).

Mechanisms Linking Microbial Communities to Host Physiology

Colonization Resistance and Epithelial Integrity

Colonization resistance is provided through competition for nutrients and attachment sites by resident microbes and inhibitory metabolites produced by resident microbes. The gut harbors an intact mucus layer, epithelial tight junctions, antimicrobial peptides and secretory immunoglobulin A which maintain a spatial separation of microorganisms from the host tissue. In the absence of competitors (due to antibiotics disrupting the ecosystem), opportunists like *C. difficile* can proliferate, especially when the ability to compete for nutrients and microbial bile acid metabolism is weakened. A rise in diversity does not indicate the restoration of barrier function; organisms and metabolic pathways responsible for that need to be identified (Feuerstadt et al. 2022, Lynch and Pedersen 2016).

Microbial Metabolites

Accessible carbohydrates are fermented to short-chain fatty acids, primarily acetate, propionate and butyrate. They are energy substrates and modulate epithelial and immune signaling, though their systemic effects will depend on the site of production, concentration, duration of exposure and host physiology. Another mechanistic connection between bacteria and disease is the secondary bile acid profile, best seen in the case of recurrent *C.*

difficile infection. Small molecules may act via host receptors, such as tryptophan derivatives. Metaflux inference from gene sequences alone can be misleading as the mere existence of a gene does not imply its expression or biological activity (Feuerstadt et al., 2022; Lynch & Pedersen, 2016).

Immune Calibration

In the host, microbe-associated molecular patterns are processed by pattern recognition receptors and are involved in the modulation of dendritic cell function, epithelial signaling and the differentiation of lymphocytes. Much of this interaction occurs in the gut-associated lymphoid tissues, such as Peyer patches, appendix and isolated lymphoid follicles, which change in structure and distribution across the intestinal tract of the human gut (Mörbe et al., 2021). Microbiological communities can induce regulatory immune programs in experimental models; other microbes or inflammatory conditions can induce effector programs. Immune homeostasis cannot be reduced to a single “beneficial” taxon or to a change in one cytokine. The outcome of a host–microbe interaction depends on host genotype, developmental stage, and diet and/or previous exposures, and can either promote tolerance or inflammation (Lynch & Pedersen, 2016).

Bidirectional Causation

Inflammation is not a by-product of dysbiosis only. Changes in oxygen availability, nitrate metabolism, secretion, transit and exposure to microorganisms due to tissue injury can select for the preservation of the disturbed ecosystem. This 2-way relationship is why it is so common in cross-sectional studies that they are unable to conclude whether the microorganism caused the disease or not. Due to the difficulties of making measurements in complex systems, mechanistic inference is more robust for longitudinal sampling, controlled interventions, and strain-resolved genomics and experimental perturbation.

The Oral Microbiome in Disease

Dental Caries and Periodontal Inflammation

Repeated acidification from frequent exposure to fermentable carbohydrates results in an ecological effect – dental caries. Over time, acid-producing and acid-tolerant organisms take a competitive advantage, demineralization occurs at a faster rate than remineralization, and clinical lesions develop. Periodontitis on the other hand is caused by a dysbiotic subgingival biofilm, which interacts with a dysregulated host inflammatory response, resulting in progressive attachment loss, and in susceptible patients, alveolar bone destruction. The study of *Porphyromonas gingivalis* and related organisms has received considerable interest, but none of these organisms can be used to explain clinical disease (Kilian et al., 2016).

Prevention of caries is still being practiced in established care using fluoride and dietary counseling, and mechanical biofilm disruption, oral hygiene and risk-factor management for periodontal disease. Commercial microbiome panels have not replaced standard clinical and radiographic assessment. Saliva-based biomarker discovery is promising, but analytical reproducibility, diagnostic thresholds and benefit to patients must be demonstrated before such tests are adopted routinely.

Oral–Systemic and Oral–Gut Links

Periodontal disease has been epidemiologically linked to the cardiometabolic outcomes, rheumatoid arthritis and systemic inflammatory states. The suggested pathways are transient bacteremia, circulating inflammatory mediators, common metabolic risk factors and changes in microbial products. However, smoking, socioeconomic status, access to oral care, diabetes, and medication use are significant confounders and observational associations cannot be interpreted as causal associations between periodontal disease and cardiovascular events.

Oral organisms survive in the gastrointestinal tract and when the stomach is irritated or its acidity is suppressed by other medication, they may survive further downstream. Oral taxa reported in colorectal lesions and stool could suggest microbial migration and ecological selection; however, the ability to track the strain to a high level of resolution is required to differentiate true transmission from closely related strains. The current state of the oral–gut axis is not that of a clinical diagnosis, but rather it is a research tool that guides mechanistic studies.

Oral Cancer

Altered oral community composition has been reported in oral squamous cell carcinoma, and the proposed mechanisms include chronic inflammation, altered microbial acetaldehyde metabolism and effects on epithelial signaling. Tumor-associated communities may also be a consequence of the lesion itself, which changes tissue oxygenation and nutrient availability. Although there are many promising advances in oral cancer diagnostics, the current methods rely on clinical examination and histopathology, and microbiome sampling is not yet a widely accepted alternative to screening. Subsequent research is needed to assess the added predictive value of microbial markers over known behavioural and clinical risk factors.

The Intestinal Microbiome in Human Disease **Inflammatory Bowel Disease**

Changes in the composition and functional capacity of intestinal microecology have been linked to Crohn disease and ulcerative colitis. Finally, in a large multicentre study of children with newly diagnosed Crohn disease (CD) without any prior treatment, mucosal biopsies taken from the ileum and rectum at the time of diagnosis were more informative of disease-associated dysbiosis than stool samples, highlighting the importance of sampling site and prior treatment (Gevers et al., 2014). The

microbial signatures seen in these patients are influenced by immune dysregulation, mucosal inflammation, nutrition, surgery and medication. It is still unclear whether a taxon is being depleted due to disease or if depletion of a taxon fosters inflammation. Current management should not be replaced by stool microbiome profiling and conventional fecal microbiota transplantation (FMT) is not recommended for the treatment of inflammatory bowel disease outside of clinical trials, according to the AGA (Peery et al., 2024).

Obesity, Diabetes and Cardiometabolic Disease

Biologically plausible links exist between the microbiome and dietary energy harvest, bile acid signaling and low-grade inflammation, thus providing a link between the microbiome and metabolic phenotypes. Some of these signatures are still present at the taxon level, but differ between cohorts regarding obesity and type 2 diabetes. Some of this heterogeneity has been attributed to the use of metformin, dietary habits, BMI, geographic location, age and glycemic status. Clinically, the evidence is not sufficient to consider replacing the current metabolic diagnostics with a commercial microbial diversity score, or consider microbiota transplantation as a standard obesity or diabetes treatment.

Colorectal Carcinogenesis

The focus in colorectal cancer research has shifted from associations of genus level microbes to identification of specific strains associated with colorectal cancer. Zepeda-Rivera et al. (2024) discovered a unique cluster of *Fusobacterium nucleatum* subsp. *animalis* (Fna C2) which was found to be enriched in colorectal tumours, and their genomic and experimental results suggested biologically plausible mechanisms. The importance of the study is that strains with the same common species name may have different colonization

ability, and different pathogenic potential. Enrichment in tumors and effects in experimental systems do not, however, establish the sensitivity, specificity or net benefit required for population screening. Microbiome tests should not displace colonoscopy or other established screening strategies.

Cancer Treatment and Immunotherapy

A growing body of research examines microbial correlates of response to immunotherapy and of treatment-related toxicity. Differences between responders and nonresponders may reflect microbial metabolites, antigen presentation, overall immune tone or concomitant medications. A predictive biomarker of this kind must be validated in the population in which it is intended to be used, and it must be shown that acting on the result improves outcomes. Until efficacy and safety are established, microbiome transfer and defined microbial consortia in oncology should remain within appropriately regulated research programs.

Gut–Brain Communication

Neural, endocrine, immune and microbial metabolite pathways support bidirectional communication between the gut and the brain. Findings from animal experiments cannot be extrapolated directly to psychiatric treatment, and human cohorts are vulnerable to confounding by diet, sleep, medication and symptom-driven behavior. Microbiome manipulation is not an established stand-alone treatment for depression, autism spectrum disorder or other neuropsychiatric and neurodevelopmental conditions, and better-controlled longitudinal and interventional studies are needed.

Drivers of Microbial Variation and Clinical Confounding

Antibiotics are among the clearest causes of rapid microbial disruption, although the effect

varies with the agent, dose, duration and baseline ecology. Proton pump inhibitors, laxatives, metformin and other medications can also alter measured gut community composition. Diet determines which substrates are available, but responses to fiber or fermented foods differ between individuals. Smoking, oral hygiene, age, oral and gastrointestinal inflammation, geography, chronic disease, bowel preparation and time of sampling all need to be considered when associations are interpreted. Host-microbe interactions are not always beneficial or detrimental and can vary by situation (Human Microbiome Project Consortium, 2012; Lynch & Pedersen, 2016).

Reverse causation is easily overlooked due to illness altering appetite, transit time and/or medication exposure. When other known variables that affect the biomarker are not equally distributed between the matched age and sex control groups, matching by age and sex alone is not adequate in clinical biomarker studies. Future studies should document drug use, timing of antibiotic exposure, diet, stool consistency, disease activity/specimen handling, and should be designed to have prespecified sensitivity analyses.

Technologies, Reproducibility and Analytical Pitfalls

Measurement Platforms

Targeted sequencing of the 16S ribosomal RNA gene is a cost-effective method for profiling a large number of bacteria and archaea, but cannot be used for viruses and fungi, and may lack taxonomic resolution depending upon the hypervariable region sequenced and the reference database. Shotgun metagenomics is a more comprehensive survey of DNA and can be used to carry out strain-level and gene-level analysis. Expressed RNA is measured by metatranscriptomics, proteins are measured by metaproteomics and biochemical end products are measured by metabolomics. The sequencing of whole genomes of pathogens or therapeutics

continues to be a vital culture test (Knight et al., 2018).

From Sequence Abundance to a Valid Biomarker

Data on relative abundance are compositional: if one taxon is increasing in apparent abundance it may actually be decreasing in absolute abundance. There are sources of batch associated artifacts such as extraction efficiency, host DNA contamination, library preparation, sequencing depth and bioinformatic parameters. Case-control studies should report negative controls, sample handling times, reference standards, appropriate correction for multiple testing and prespecified validation criteria. A classifier that performs well in a discovery cohort may fail when it is transferred to other centers, populations or sequencing platforms (Knight et al., 2018; Mirzayi et al., 2021).

The STORMS checklist provides recommendations for the transparent reporting of human microbiome studies, and STREAMS extends reporting guidance to environmental, synthetic and non-human host-associated microbiome research (Kelliher et al., 2025; Mirzayi et al., 2021). Neither checklist replaces a study-specific assessment of risk of bias. Studies intended to justify clinical action also require independent external validation, calibration, defined decision thresholds, health-economic assessment and evidence that patient outcomes improve.

Microbiota-Directed Prevention and Treatment

Recurrent *Clostridioides difficile* Infection: Established Clinical Translation

Recurrent *C. difficile* infection is the clearest current example of microbiome restoration entering regulated clinical use. In selected patients who have completed antibiotic therapy, microbiota-based strategies aim to re-establish colonization resistance. The FDA has approved fecal microbiota, live-jslm (REBYOTA) and

fecal microbiota spores, live-brpk (VOWST) for the prevention of recurrence in adults following antibacterial treatment for recurrent infection (U.S. Food and Drug Administration [FDA], n.d.-a, n.d.-b). Both products are indicated to prevent recurrence; neither is indicated for the treatment of an active episode of *C. difficile* infection.

In the phase 3 randomized trial of SER-109, the investigational product later approved as fecal microbiota spores, live-brpk, recurrence within 8 weeks occurred in 12% of patients in the SER-109 group and in 40% of those who received placebo after standard antibiotic treatment (Feuerstadt et al., 2022). This is an important success, but the result applies to the trial population and the treatment protocol used. The 2024 AGA guideline suggests the selective use of fecal microbiota-based therapies after completion of standard antibiotics in immunocompetent adults with recurrent infection, and it gives separate advice for immunocompromised patients and for severe or fulminant infection that does not respond to antibiotics (Peery et al., 2024). Products produced from human faeces need to be carefully managed for the risk of infection, patient suitability and regulated manufacturing processes.

Why Indications Cannot Simply Be Generalized

FMT has been studied in ulcerative colitis, Crohn disease, pouchitis and irritable bowel syndrome, but there are some inconsistencies between studies and the risk/benefit ratio is unclear, making it difficult to draw general recommendations for use in clinical practice. The 2024 AGA guideline recommends against the use of conventional FMT for these conditions (except for clinical trials) (Peery et al., 2024). Guidelines do not be superseded by positive findings in small pilot studies. For very immunocompromised patients, there may be a higher risk of infectious transmission, thus

underscoring the importance of making individual decisions by specialists.

Food, Fiber and Prebiotics

Dietary fibre provides substrates for fermentation and may help support beneficial microbial metabolic functions, although this will vary depending on the type of dietary fibre, background diet and individual's existing microbial community. General nutrition recommendations based on sound nutrition science are fine, but those which state that a supplement will “reset” the microbiome or cure systemic disease are not. Intervention studies should not only measure changes in microbial populations but also health outcomes.

Probiotics, Synbiotics, Postbiotics and Precision Approaches

Probiotics are live microorganisms that when ingested in appropriate quantities provide a health benefit to the host, while prebiotics are substrates that are selectively utilized by microorganisms that are present in the host. Synbiotics are combinations of live microorganisms and these substrates, while

postbiotics are inanimate microorganism and/or their components that have proven to provide health benefits. The activity of each of these products depends on the strain, formulation, population and endpoint used, and cannot be extrapolated from one organism to the others of the same commercial category. Engineered consortia, bacteriophages and targeted metabolites provide research opportunities but must be subjected to traditional test of safety, efficacy, delivery and ecological effects.

Current Evidence by Clinical Domain

The current state of the microbiome evidence in the clinical areas highlighted above is summarized in Table 1, along with the key limitation that should be considered in interpreting the evidence in each area. The evidence for research or ecology-informed standard care, but not microbiome-guided clinical decisions, for the rest of the domains is available, with only one domain (recurrent *C. difficile* infection) having reached regulatory therapeutic use.

Table 1. Evidence-to-Practice Summary of Microbiome Applications by Clinical Domain

Clinical domain	Translational status	What current evidence supports	Main limitation and prudent interpretation
Recurrent <i>C. difficile</i> infection	Established (regulated clinical use)	Post-antibiotic, microbiota-based prevention of recurrence in selected adults (Feuerstadt et al., 2022; Peery et al., 2024; FDA, n.d.-a, n.d.-b)	Patient selection, safety screening and the approved product indication must be respected
Dental caries and periodontitis	Established (ecology-informed standard care)	Biofilm ecology informs prevention and established dental care (Kilian et al., 2016)	Routine sequencing does not replace clinical and radiographic diagnosis
Inflammatory bowel disease	Investigational	Disease-associated microbial ecology and mechanistic research (Gevers et al., 2014)	AGA suggests against conventional FMT outside clinical trials (Peery et al., 2024)

Clinical domain	Translational status	What current evidence supports	Main limitation and prudent interpretation
Colorectal cancer	Investigational	Tumor-associated strain-level signals, including Fna C2 (Zepeda-Rivera et al., 2024)	Not a validated stand-alone screening or therapeutic test
Metabolic and neuropsychiatric disease	Investigational	Plausible biological pathways and observational associations	No universal diagnostic microbiome threshold; no routine transfer therapy
Cancer immunotherapy	Investigational	Candidate microbial signatures associated with treatment response	External validation and evidence of interventional benefit are still required

Note. AGA = American Gastroenterological Association; FDA = U.S. Food and Drug Administration; FMT = fecal microbiota transplantation; Fna C2 = *Fusobacterium nucleatum* subsp. *animalis* clade 2. Translational status reflects the authors' synthesis of the cited evidence and is not a formal GRADE certainty rating.

DISCUSSION

Implementation Considerations for Clinical Microbiome Evidence

A clinically useful claim must specify the intended population, collection site, assay, decision threshold, comparator and patient-centered outcome. For diagnostic tests, discrimination in a discovery cohort is not enough; external validation in other geographic settings, calibration, preanalytical reproducibility and incremental value over standard clinical predictors must also be shown. For therapies, engraftment or a change in bacterial composition is a mechanistic measure, not proof of clinical benefit. Randomized studies should conduct surveillance for adverse events, duration of response, other concurrent drugs and clinically relevant endpoints, especially when administered to immunocompromised individuals (Feuerstadt et al., 2022; Knight et al., 2018; Mirzayi et al., 2021; Peery et al., 2024).

Taxonomic biomarker vs. mechanistic target is also important. A taxon related to disease could just be a proxy for diet, mucosal inflammation or exposure to antibiotics. If it is to be targeted therapeutically, evidence must be presented that establishes a correlation between the strain-level function and the pathology, and that intervening

alters the outcome. This chain of evidence is more rigorous than a cross sectional case–control comparison and contains safeguards for patients and health systems from hasty implementation of low-value microbiome testing (Knight et al., 2018; Lynch & Pedersen, 2016; Zepeda-Rivera et al., 2024).

Research Priorities

The evidence reviewed here yields a number of priorities. Observational studies should be longitudinal studies that include appropriate comparator groups, to allow microbial changes prior to disease to be distinguished from the changes that follow inflammation and drug exposure. Second, measurements should be more functionally informative, by incorporating metagenomic signatures with metabolomics, culture and host phenotyping, as well as strain-level analysis. Third, intervention trials should include clinically relevant endpoints, not surrogate endpoints, and adequate monitoring for adverse events, should these be relevant, should be done in advance of the analysis of the data.

Fourth, sampling and analytical procedures need to be harmonized across centers; STORMS provides a reporting framework for human microbiome studies, whereas STREAMS addresses environmental, synthetic and non-

human host-associated communities (Kelliher et al., 2025; Mirzayi et al., 2021). Fifth, cohorts should consist of many people from various geographic, ethnic, socioeconomic and nutritional backgrounds and should measure the performance of predictive models in resource-limited laboratory settings. Lastly, safety, access, manufacturing regulations, transfer of antimicrobial resistance, patient privacy and reimbursement should be evaluated in concert with biological activity. The requirements are especially important when dealing with any form of therapy that places living microbial communities in medically fragile people.

Geographic Generalizability and Translational Equity

Microbiome reference datasets are not equally representative of all diets and medication usage, as well as socioeconomic exposures and care environments. Both biological differences and batch effects can cause a microbial classifier developed in one population to give poor performance in another population. When collaboration between international partners is involved, transportability should be considered in the future, context-specific reference intervals should be established when warranted, and the involvement of non-bacterial community members (when applicable) should be reported. The use of expensive assays in resource-limited settings is an assumption and should not be done without evidence that these assays are superior to conventional assays in improving decisions. (Knight et al., 2018; Mirzayi et al., 2021).

Strengths and Limitations of the Review

The review is an integration of ecological concepts with an explicit evidence hierarchy and a clinically-oriented distinction between established therapy and promising hypotheses. It has a strong emphasis on the oral and intestinal microbiota, and it widens the scope to a broader spectrum of diseases as well as to a translational agenda. The primary drawbacks are its purposive narrative search, non-

systematic screening and risk of bias assessment and the potential for new studies or regulatory decisions to alter clinical practice. Some mechanistic sections summarize complex bodies of literature rather than providing quantitative meta-analytic conclusions. Variation in sampling sites, host exposures, study populations and study designs should also be taken into account when the evidence summarized here is interpreted.

CONCLUSION

The human microbiome is neither a single organ nor a fixed list of optimal microorganisms. It is a collection of site-specific ecosystems connected to host physiology through biochemical, immunological and ecological interactions. Changes in oral and intestinal communities offer mechanistic insight into many diseases, but a consistent association does not by itself establish causality or clinical actionability. The strongest clinical translation to date is microbiota-based prevention of recurrent *C. difficile* infection in carefully selected adults, whereas most applications in oncological, metabolic, inflammatory and neurological disease remain experimental. Further progress will depend on strain- and function-resolved research, rigorous external validation, careful safety assessment and trials that demonstrate benefit to patients.

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Author contributions: Liqaa H. Naser: conceptualization, methodology, writing – original draft, supervision and project administration. Zinah Zwaini: investigation (literature search and selection), validation of sources and writing – review and editing. Dina

Hussain Hatif Almansoori: data curation, visualization (Table 1) and writing – review and editing. All authors read and approved the final manuscript.

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