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# Microbiome-Targeted Therapies in Gastrointestinal Diseases: Clinical Evidence and Emerging Innovations

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**Abstract**

Microbiome-targeted therapies are redefining gastroenterology by delivering precision interventions that align with the body's natural microbial ecosystem. This narrative review evaluates evidence for established approaches, probiotics, prebiotics, fecal microbiota transplantation (FMT), and postbiotics, and examines emerging innovations such as engineered probiotics, bacteriophage therapy, and metabolite-based interventions. Cure rates for recurrent Clostridium difficile infection in randomized trials range from 67% to 94%, depending on route and donor protocol, while multi-strain probiotics provide moderate benefits in inflammatory bowel disease. New modalities, including engineered bacteria and defined bacterial consortia, have progressed to Phase 3 trials, with several granted FDA breakthrough therapy designation. Approvals of Rebyota and Vowst mark a pivotal milestone, creating validated regulatory pathways for microbiome therapeutics. Despite progress, challenges remain in protocol standardisation, patient selection, cost-effectiveness, and clinical integration. Over 200 active trials and growing pharmaceutical investment signal a robust pipeline, with applications expanding to oncology, metabolic disorders, and immune modulation. Continued progress depends on validated biomarkers and personalized strategies guided by microbiome profiling. International regulatory harmonization will also be required to ensure safe and equitable adoption. The field is shifting toward working with, rather than against, the body's microbial ecosystem, offering substantial potential for personalized gastrointestinal disease management.

**Keywords:** microbiome therapeutics; probiotics; fecal microbiota transplantation; gastrointestinal disease; precision medicine



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## 1. Introduction

The human gastrointestinal tract harbours trillions of microorganisms that profoundly influence health and disease through complex interactions with host physiology, metabolism, and immune function [1]. Disruptions in this delicate microbial ecosystem, known as dysbiosis, contribute to a range of gastrointestinal disorders, from functional conditions to inflammatory diseases and infections [1]. Traditional therapeutic approaches often fail to address underlying microbial imbalances, leading to symptom recurrence and treatment resistance. Microbiome-targeted therapies offer a paradigm shift toward precision interventions that restore microbial balance and enhance therapeutic outcomes [2]. These approaches range from established interventions, such as probiotics and fecal microbiota transplantation, to cutting-edge innovations, including engineered bacteria and

metabolite-based therapies [2]. Recent U.S. Food and Drug Administration (FDA) approvals of the first microbiome-derived pharmaceuticals mark a pivotal transition from experimental treatments to validated clinical interventions.

This review aims to provide a comprehensive analysis of current clinical evidence for microbiome-targeted therapies across major gastrointestinal diseases, examine emerging therapeutic innovations, and evaluate practical considerations for clinical implementation. We focus on clinical outcomes data, comparative effectiveness studies, and real-world implementation experiences while highlighting future directions in this rapidly advancing field.

## 2. Methods

This narrative review was conducted as a narrative synthesis of recent clinical and translational evidence. Structured literature searches were carried out across PubMed/MEDLINE, Cochrane, ClinicalTrials.gov, EMBASE, Web of Science, and Scopus for the period January 2015 to August 2025. The following combined search terms were used: "microbiome", "gut microbiota", "probiotics", "prebiotics", "synbiotics", "postbiotics", "fecal microbiota transplantation", "FMT", "engineered probiotics", "bacteriophage", "metabolite therapy", "gastrointestinal disease", "inflammatory bowel disease", "irritable bowel syndrome", "Clostridioides difficile", "non-alcoholic fatty liver disease", "NAFLD", "NASH", "Helicobacter pylori".

Additional disease-specific terms were added to refine searches. Reference lists of relevant systematic reviews and meta-analyses were hand-searched to identify further eligible studies. Priority was given to randomized controlled trials, systematic reviews, meta-analyses, regulatory documents (FDA, EMA), and guideline statements from major gastroenterology societies.

Inclusion criteria were: peer-reviewed English-language publications, clinical trials and reviews reporting patient outcomes, and regulatory or guideline documents addressing microbiome-targeted therapies. Exclusion criteria were: case reports, single-patient studies, preclinical-only studies, conference abstracts, and non-English publications.

Evidence was synthesized qualitatively, with emphasis on clinical relevance, magnitude of effect, and translational implications. Where available, pooled estimates from high-quality meta-analyses and regulatory submissions were prioritized to reflect evidence strength.

## 3. Established Therapeutic Approaches

### *3.1. Fecal Microbiota Transplantation Leads to Clinical Efficacy*

Fecal microbiota transplantation represents the most clinically validated microbiome intervention, with robust evidence across multiple conditions. The most compelling results emerge from *C. difficile* infection treatment, where FMT demonstrates superior clinical outcomes compared to standard antibiotic therapies [1,2]. Meta-analyses demonstrate that fecal microbiota transplantation (FMT) is highly effective for the treatment of recurrent and refractory Clostridium difficile infection. In a systematic review and meta-analysis, Quraishi et al. [3] reported markedly higher cure rates with FMT compared to conventional antibiotic therapy. Similarly, Fischer et al. [4] found FMT to be both safe and efficacious for patients with inflammatory bowel disease who developed recurrent or refractory *C. difficile* infection. Cure rates for recurrent Clostridium difficile infection (CDI) in randomized trials range from 67% to 94%, depending on delivery route and donor protocol [1,3]. Most studies define cure as absence of recurrence within 8–12 weeks. Meta-analyses report an absolute risk reduction of about 30% compared with vancomycin, yielding a number needed to treat between 3 and 5 [2,3].

Recent randomised controlled trials have provided further insight into microbiome-based therapies. In the ECOSPOR III trial, Feuerstadt et al. [5] demonstrated that the investigational oral microbiome therapeutic SER-109 significantly reduced the risk of *C. difficile* recurrence compared with placebo. Clinical guidelines from the American College of Gastroenterology summarise these and other high-quality studies, underscoring the role of FMT in current practice [6]. Safety profiles remain favourable across studies. Wang et al. [7] reported serious adverse events in fewer than 11% of patients receiving FMT, with rates similar to those observed in other gastrointestinal interventions. The most commonly reported side effects include transient abdominal discomfort, diarrhoea, and bloating. Following documented cases of pathogen transmission during FMT, including transmission of drug-resistant Escherichia coli described by DeFilipp et al. [8], enhanced donor screening protocols have been implemented to further mitigate risk.

### *3.2. Probiotics and Condition-Specific Benefits*

Probiotics demonstrate variable efficacy across gastrointestinal conditions, with the strongest signals in specific clinical scenarios. In irritable bowel syndrome, a systematic review and meta-analysis of 53 randomised controlled trials involving 5545 patients found that selected probiotics improve global symptoms and abdominal pain. However, conclusions were limited by heterogeneity and variable certainty [9]. Efficacy is strain- and disease-specific. For IBS, Lactobacillus plantarum 299v and Bifidobacterium infantis 35624 have the most consistent supportive evidence, while results for other single-strain and multi-strain products are mixed [10].

For inflammatory bowel disease, meta-analysis indicates that some probiotics, particularly multi-strain formulations such as VSL#3, can be beneficial in ulcerative colitis, although effect sizes and certainty vary, and optimal dosing is not established by the included studies [11]. For maintenance of remission in ulcerative colitis, a Cochrane review concluded that overall effectiveness remains uncertain due to low to very low-certainty evidence [12]. In pouchitis after ileal pouch–anal anastomosis, the evidence base for probiotics and other microbiome-targeted options is limited and uncertain, and available reviews do not provide a robust ranking that places multi-strain probiotics among the top options for preventing clinical relapse [13]. Substantial heterogeneity exists across trials due to differences in probiotic strain, dose, treatment duration, and outcome measures. These factors limit pooled estimates and explain divergent conclusions. Null findings occur frequently and should be considered alongside positive results to avoid overstating efficacy.

### *3.3. Prebiotics and Synbiotics Expand Therapeutic Options*

Prebiotic interventions, defined as substrates selectively utilised by host microorganisms conferring a health benefit, have shown benefits in a variety of conditions, including functional gastrointestinal disorders. Evidence supports their role in modulating specific microbial metabolic pathways, though clinical outcomes vary across studies [14]. Synbiotic formulations, which combine probiotics with prebiotic substrates, are designed to enhance probiotic survival and colonisation in the gut. Limited emerging evidence suggests they may offer advantages over probiotic use alone. However, current research is constrained by heterogeneous study designs and the absence of standardised protocols and outcome measures [15].

## 4. Disease-Specific Clinical Applications

### 4.1. Inflammatory Bowel Disease Treatment Advances

Inflammatory bowel disease is a priority area for microbiome interventions, but current guideline recommendations are conservative. The AGA advises that probiotics for ulcerative colitis or Crohn's disease should be used only within clinical trials, with a conditional (very low-certainty) suggestion limited to a specific 8-strain formulation in pouchitis [16]. A meta-analysis of Crohn's disease found no significant benefit of probiotics in maintaining remission, underscoring that their applications in this setting remain investigational [17]. Randomised trials of FMT in ulcerative colitis demonstrate that multidonor, intensive-dosing regimens can induce remission in a subset of patients. In Paramsothy et al., 2017, steroid-free clinical remission with endoscopic improvement at 8 weeks was achieved in about 27% of patients receiving FMT versus ~8% receiving placebo [18]. Multidonor, intensive regimens have induced remission in about 25–30% of patients [18]. However, reproducibility is limited and optimal protocols remain undefined. Protocol heterogeneity continues to limit conclusions on optimal regimens. Beyond IBD, FMT has also been explored in other gastrointestinal disorders, such as slow transit constipation, where a small pilot study suggested potential symptomatic benefits [19]. These findings illustrate the broader therapeutic interest in microbiome-directed approaches while highlighting the need for standardised protocols and validated outcome measures before routine clinical use in IBD [16–19]. Despite some positive findings in ulcerative colitis and pouchitis, the evidence for probiotics in IBD remains of low certainty, with small sample sizes, heterogeneous trial designs, and limited reproducibility reducing confidence in their clinical utility.

### 4.2. Clostridium Difficile Infection Management

*C. difficile* infection is the flagship indication for microbiome therapeutics, as reflected by regulatory approvals and clinical guideline recommendations. For primary prevention, a Cochrane review found that probiotics reduce the risk of antibiotic-associated *C. difficile*-associated diarrhoea in adults and children, though evidence on prevention of recurrence was insufficient [20]. FDA-approved microbiome-based products show consistent efficacy in preventing recurrence: Vowst reduced 8-week recurrence to 12.4% compared with 39.8% for placebo [21], and Rebyota achieved treatment success at 8 weeks in 70.6% of recipients versus 57.5% with placebo [22]. Current IDSA/SHEA treatment guidelines recommend FMT for multiply recurrent CDI after failure of appropriate antibiotic regimens, with fidaxomicin and vancomycin as standard antimicrobial options [23].

### 4.3. Irritable Bowel Syndrome Symptom Management

IBS is a heterogeneous condition, and microbiome interventions show variable but sometimes meaningful benefits. Recent randomised controlled trials, summarised in a systematic review, found that certain probiotic regimens improve IBS symptoms compared with a placebo, with multi-strain formulations tending to perform better than single-strain products. However, effect sizes and study designs varied [24]. Efficacy is strain-specific. An evidence-based international guide identified particular preparations with supportive data for IBS outcomes, including specific Bifidobacterium strains such as *B. infantis* 35624 for global symptoms and abdominal pain; this review did not assess Saccharomyces cerevisiae I-3856 [25].

Regarding treatment duration, trials reviewed in [24] more often demonstrated significant improvements with interventions lasting at least eight weeks, suggesting that benefits may require sustained administration rather than very short courses [26]. Quantitative pooled estimates vary across analyses. An earlier systematic review reported a relative risk of persistent global symptoms of approximately 0.71 for probiotics versus placebo,

corresponding to a number needed to treat of approximately four; however, heterogeneity was substantial, and optimal strains or doses could not be identified [26]. Safety profiles for probiotics remain favourable. Large-scale meta-analyses in other gastrointestinal contexts, such as antibiotic-associated diarrhea, have found no significant increase in adverse events compared with placebo, supporting their overall tolerability [27]. Despite this safety profile, evidence of clinical efficacy in IBS remains low certainty because of small sample sizes, heterogeneous trial designs, and limited reproducibility.

### *4.4. Metabolic Liver Disease Interventions*

Non-alcoholic fatty liver disease (NAFLD) is emerging as a target for microbiome-based interventions, with growing but still limited clinical evidence. Reviews of clinical studies report improvements in liver enzymes, inflammatory markers, and imaging-based assessments of hepatic steatosis and stiffness in some probiotic and FMT trials. However, robust meta-analytic confirmation is lacking [28]. Mechanistic insights from microbiome data have identified NAFLD-associated microbial signatures and predicted metabolic pathway changes, including altered profiles of gut-derived metabolites [29]. Probiotics containing butyrate-producing species have demonstrated beneficial effects on hepatic steatosis and liver enzyme levels in randomised controlled trials, with anti-inflammatory effects, such as reductions in high-sensitivity C-reactive protein. Proposed mechanisms include enhanced short-chain fatty acid production, although this has not always been directly measured [30]. Animal models consistently demonstrate therapeutic benefit, but human evidence remains limited to small randomized or pilot trials [31]. Translation to clinical practice is therefore still preliminary.

### *4.5. Helicobacter Pylori Eradication Enhancement*

*H. pylori* eradication therapy can benefit from probiotic adjuncts, with multiple meta-analyses, some focused on paediatric populations, showing modest increases in eradication rates and reductions in antibiotic-associated adverse effects, particularly diarrhoea [32–35]. In children, Lactobacillus-supplemented triple therapy has been associated with improved outcomes compared to standard therapy alone [32]. A broader paediatric meta-analysis likewise supports the use of probiotics as an add-on during eradication regimens [33]. Across trials synthesised in these reviews, Lactobacillus and Saccharomyces boulardii are the most consistently studied adjuncts; both are associated with higher eradication rates and fewer overall side effects compared with antibiotics alone [34,35]. Strain-specific superiority (e.g., Bifidobacterium vs. others) cannot be concluded from these citations, and effect sizes vary by study design and population [32–35]. In practice, the improved tolerability observed with probiotic co-therapy may help support adherence and reduce antibiotic-associated complications, even as absolute gains in eradication remain modest and strain- and regimen-dependent [34,35].

A summary of the evidence for microbiome-targeted therapies across major gastrointestinal conditions, including their clinical outcomes, evidence strength, and limitations, is presented in Tables 1 and 2.

**Table 1.** Summary of Clinical Evidence for Microbiome-Targeted Therapies Across Gastrointestinal Conditions.

| Condition | Intervention | Key Findings | Evidence Strength (GRADE) | Limitations/Notes |
|---|---|---|---|---|
| **Inflammatory Bowel Disease (IBD)** | Probiotics | AGA: Use only in clinical trials for UC/CD; conditional (very low-certainty) suggestion for 8-strain mix in pouchitis [16]. No significant benefit in Crohn's remission maintenance [17]. | Very low–low | Benefit limited to specific strains/formulations; remains investigational. |
| | FMT (UC) | Multidonor, intensive regimens induced steroid-free remission with endoscopic improvement in ~27% vs. ~8% placebo at 8 weeks [18]. | Moderate | Protocol heterogeneity; optimal regimens unclear. |
| | FMT (Other GI) | Small pilot study in slow transit constipation showed potential benefit [19]. | Very low | Small sample sizes; preliminary data only. |
| **Clostridium difficile infection (CDI)** | Probiotics (Primary prevention) | Cochrane review: reduced risk of antibiotic-associated CDI; insufficient data for recurrence prevention [20]. | Moderate | Prevention effect mostly in primary setting. |
| | FDA-approved microbiome products | Vowst: recurrence 12.4% vs. 39.8% placebo [21]; Rebyota: success 70.6% vs. 57.5% placebo [22]. | High | Specific to recurrent CDI; long-term durability still being studied. |
| | FMT | Recommended by IDSA/SHEA for multiply recurrent CDI after antibiotic failure [23]. | High | Requires donor screening; procedural infrastructure needed. |
| **Irritable Bowel Syndrome (IBS)** | Probiotics | Multi-strain > single strain for symptom improvement; e.g., *B. infantis* 35624 effective for global symptoms/abdominal pain [24,25]. | Low–Moderate | Strain-specific effects; optimal dose/duration unclear. |
| | Treatment duration | ≥8 weeks associated with better outcomes [26]. | | Short courses less effective. |
| | Safety | No increased adverse events vs. placebo in large GI meta-analyses [27]. | High | Well-tolerated across trials. |
| **Metabolic Liver Disease (NAFLD/NASH)** | Probiotics | Some RCTs show improvements in liver enzymes, steatosis, inflammatory markers [28,30]. | Low–Moderate | Meta-analytic confirmation lacking. |
| | FMT | Early pilot data suggest benefit; animal models support potential [29,31]. | Very low | Human translation at early stage. |

**Table 1.** *Cont.*

| Condition | Intervention | Key Findings | Evidence Strength (GRADE) | Limitations/Notes |
|---|---|---|---|---|
| ***Helicobacter pylori*** | Probiotic adjuncts to eradication therapy | Modest increase in eradication rates; reduced antibiotic-associated diarrhoea [34,35]. | Moderate | Effects strain- and regimen-dependent. |
| | Strains studied | *Lactobacillus* spp., *S. boulardii* most consistent; paediatric triple therapy with *Lactobacillus* improved outcomes [32,33]. | | No clear strain superiority established. |

This table summarises the current clinical evidence for microbiome-targeted interventions across major gastrointestinal disease areas, highlighting intervention types, key findings, evidence strength, and limitations; Abbreviations: AGA—American Gastroenterological Association; UC—ulcerative colitis; CD—Crohn's disease; CDI—Clostridium difficile infection; FMT—fecal microbiota transplantation; GI—gastrointestinal; IDSA/SHEA—Infectious Diseases Society of America/Society for Healthcare Epidemiology of America; NAFLD—non-alcoholic fatty liver disease; NASH—non-alcoholic steatohepatitis; RCT—randomised controlled trial.

**Table 2.** Summary of evidence characteristics for key microbiome-targeted therapies in gastrointestinal disease.

| Condition | Intervention | Sample Size/Follow-Up | Evidence Source | Evidence Strength (GRADE) |
|---|---|---|---|---|
| **Recurrent CDI** | FMT (various delivery routes) | RCTs: 40–232 patients; 8–12 weeks follow-up [3] | RCTs + Meta-analysis | High |
| | Vowst (SER-109) | Phase 3 RCT: 182 patients; 8 weeks [5] | Regulatory trial (FDA submission) | High |
| | Rebyota (RBX2660) | Phase 3 RCTs + pooled analysis: ~270 patients; 8 weeks [22] | Regulatory trial + integrated analyses | High |
| **Ulcerative colitis** | Multidonor intensive FMT | RCT: 81 patients; 8 weeks [18] | RCT | Moderate |
| **Inflammatory Bowel Disease** | Probiotics (VSL#3/multi-strain) | Trials 50–200 patients; 8–52 weeks [16,17] | RCTs + Cochrane reviews | Low–very low |
| | Probiotics (various strains) | Trials 80–400 patients; 4–12 weeks [9,24] | RCTs + Systematic reviews | Low–moderate |
| ***H. pylori* eradication** | Adjunct probiotics (Bifidobacterium-based) | RCTs ~200 patients; 4–8 weeks [30] | RCTs | Low–moderate |

Abbreviations: CDI—Clostridium difficile infection; FMT—fecal microbiota transplantation; RCT—randomised controlled trial; VSL#3—Proprietary 8-strain high-potency probiotic formulation (originally produced by VSL Pharmaceuticals; now marketed as Vivomixx® or Visbiome®).

## 5. Emerging Therapeutic Innovations

### *5.1. Engineered Probiotics Enter Clinical Development*

Next-generation probiotics built with synthetic biology represent an advanced frontier in microbiome therapeutics. Engineered organisms have been developed with programmable therapeutic functions, improved stability, and targeted delivery features [36,37]. Current research includes the design of sense-and-respond systems in probiotics to detect pathogen-associated signals and release antimicrobial agents, as outlined in conceptual frameworks for synthetic microbes as drug delivery platforms [38]. Applications in metabolic diseases include engineered strains capable of producing therapeutic enzymes, such as phenylalanine ammonia lyase, for phenylketonuria [39].

SYNB1618, based on *E. coli* Nissle 1917 and engineered with phenylalanine-degrading pathways, demonstrated safety, tolerability, and pharmacodynamic activity in early-phase human trials [40]. Safety innovation strategies described for engineered probiotics include antibiotic resistance-free selection systems, genetic kill switches, and other containment approaches [41]. CRISPR-Cas9 technology further enables precise, sequence-specific genetic targeting of bacteria, supporting the development of highly controlled therapeutic functions [42]. Published human trials report only early safety and pharmacodynamic outcomes. No Phase 3 efficacy data are yet available. Regulatory approval will depend on robust biosafety safeguards, including genetic containment strategies and mechanisms to minimize unintended ecological effects.

### *5.2. Bacteriophage Therapy Development*

Bacteriophage-based approaches offer targeted antimicrobial options against gastrointestinal pathogens, including Clostridioides difficile. Endolysins derived from *C. difficile* phages have demonstrated activity in vitro and in infection models, supporting their potential as precision adjuncts to existing therapies [43,44]. Technical strategies under investigation include combining multiple phages to broaden host-range and reduce the emergence of resistance, as demonstrated by phage cocktails that curtailed *C. difficile* growth in vitro and limited proliferation in vivo models [45]. The CD27L endolysin, cloned from a *C. difficile* bacteriophage, exhibits lytic activity against *C. difficile* with selectivity that helps spare commensal bacteria in experimental settings [44]. Clinical development remains early-stage. Human studies have primarily evaluated the safety and tolerability of orally administered phage preparations, which appear acceptable in healthy adults; formulation and dosing considerations (including survival through the gastrointestinal tract) are active areas of work [46,47]. Overall, preclinical findings, including infection-model data with *C. difficile* endolysins, support continued development, but robust clinical efficacy data are still limited [43–47]. Human efficacy data remain absent, with formulation stability and resistance risk as major hurdles. For bacteriophage therapies, effective resistance monitoring and stability controls will be critical to meet regulatory standards and ensure safe clinical translation.

### *5.3. Metabolite-Based Interventions Advance*

Microbial metabolite-based strategies aim to influence specific host—microbe biochemical pathways. Short-chain fatty acids (SCFAs) such as butyrate, propionate, and acetate have well-described roles in gut health, metabolic regulation, and immune modulation, with proposed applications in gastrointestinal and metabolic diseases [48,49]. Bile acid metabolism is another promising target, as microbially modified bile acids can act as farnesoid X receptor (FXR) agonists, influencing metabolic homeostasis and liver function [50]. Tryptophan-derived indole metabolites activate the aryl hydrocarbon receptor, enhancing mucosal immunity and supporting intestinal barrier integrity. Reduced levels of microbiota-derived metabolites, including secondary bile acids and tryptophan catabolites, have been associated with loss of colonization resistance, intestinal inflammation, and increased risk of disorders such as inflammatory bowel disease and metabolic dysfunction [51–53]. Postbiotic approaches are being explored for their safety, stability, and defined composition advantages compared with live microorganisms. Akkermansia muciniphila is among the candidates investigated for metabolic and gut barrier benefits [54]. The ISAPP consensus defines postbiotics broadly and summarises evidence for beneficial effects on gut barrier function and immune modulation, while noting that clinical outcomes depend on the specific preparation and context [55].

Defined metabolite supplements differ from complex postbiotic mixtures, which face regulatory uncertainty due to variable composition.

A summary figure (Figure 1) maps the developmental stage, mechanisms of action, and key translational hurdles for engineered probiotics, bacteriophage therapies, and metabolite-based interventions, highlighting the current opportunities and barriers to clinical adoption.

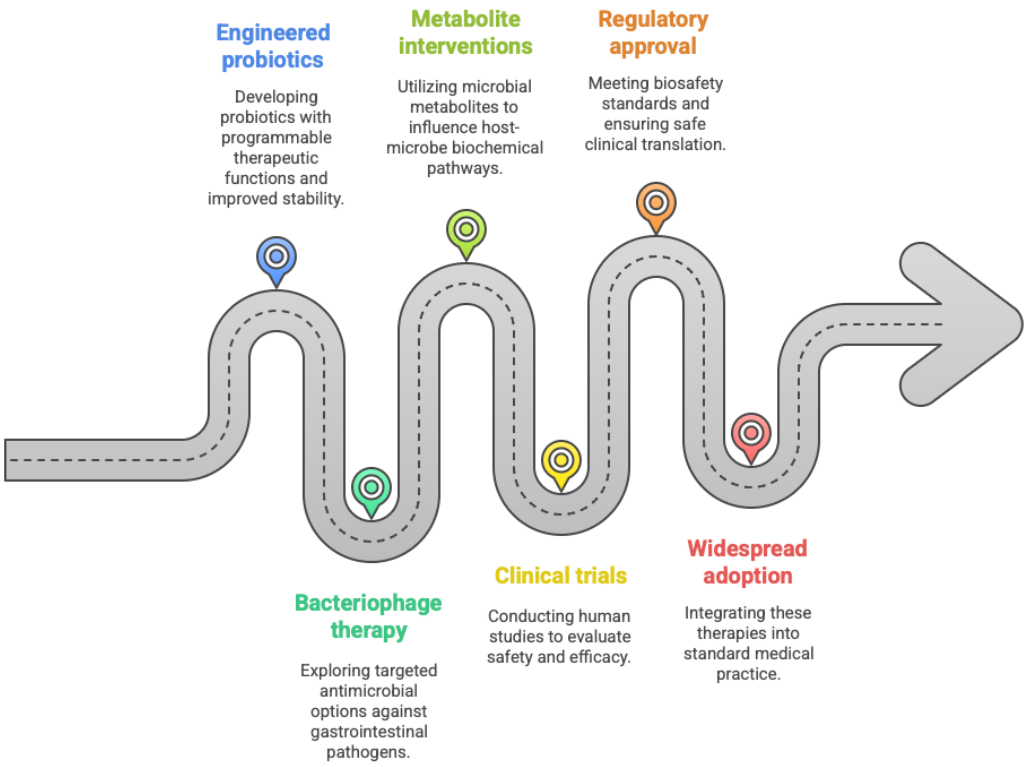


**Figure 1.** Developmental stage, mechanisms of action, and translational hurdles of emerging microbiome-targeted innovations.

## 6. Regulatory Landscape and Clinical Implementation

### *6.1. FDA Approvals Establish Therapeutic Validation*

The November 2022 approval of Rebyota and the April 2023 approval of Vowst marked watershed moments for microbiome therapeutics, representing the first FDA-approved microbiota-based products for gastrointestinal indications and establishing recognised regulatory pathways [56,57]. Rebyota is a donor-derived fecal microbiota preparation administered as a single-dose rectal enema. Clinical trials have demonstrated superiority over placebo for prevention of recurrent Clostridium difficile infection, with published data from pivotal studies supporting its approval [58]. Vowst contains purified live Firmicutes spores sourced from qualified donors, delivered as oral capsules taken over three consecutive days, and achieved 12.4% recurrence versus 39.8% with placebo at 8 weeks in its pivotal study [59].

Vowst received Breakthrough Therapy, Priority Review, and Orphan Drug designations, reflecting its significant clinical advantages over existing treatments. Both products are regulated under the FDA's framework for biologics, with the Live Biotherapeutic Products guidance from the Center for Biologics Evaluation and Research providing relevant chemistry, manufacturing, and control expectations [60]. Additional donor screening requirements, including enhanced pathogen testing such as for COVID-19, have been implemented following safety alerts [61]. The manufacturing of these products must comply

with current Good Manufacturing Practice standards, with comprehensive quality control systems in place [62].

### *6.2. Cost-Effectiveness Challenges Implementation*

High acquisition costs remain a barrier to broad adoption despite clinical efficacy. The Institute for Clinical and Economic Review (ICER) lists estimated wholesale acquisition costs of approximately $17,500 per treatment course for Vowst and $9500 for Rebyota, compared with substantially lower procedural costs for conventional fecal microbiota transplantation [63]. Insurance coverage varies by plan and region. UnitedHealthcare policy documents confirm coverage of fecal microbiota transplantation, including product-based preparations, starting at first recurrence for eligible beneficiaries [64]. Manufacturer-reported patient support programs offer co-pay assistance of up to $5000–$10,000 annually for eligible insured patients [65,66]. Patient assistance programs provide a no-cost product to qualifying uninsured patients. Specialty pharmacy networks manage product distribution and offer benefits verification and reimbursement support, which may assist in navigating prior authorisation processes [65,66]. Costs should also be considered in the context of existing gastrointestinal therapies. Traditional FMT in procedural settings may cost under USD 1500, far less than Rebyota or Vowst. Their relative value depends on long-term durability of benefit and payer support. Conventional treatments such as vancomycin for recurrent CDI or immunosuppressants for IBD remain far less costly, whereas biologics carry high but reimbursed prices. Framing microbiome therapies against these benchmarks highlights both their therapeutic promise and economic challenge.

### *6.3. Implementation Barriers Require Systematic Solutions*

Clinical implementation faces several practical considerations, including storage requirements, administration procedures, and provider training. Rebyota must be stored in a dedicated freezer at −20 °C or colder and used within seven days after thawing if kept refrigerated [67]. Vowst, as an oral capsule formulation, follows standard oral medication handling procedures without requiring special cold storage needs, with stability features designed for routine pharmacy use [68]. Successful integration into care pathways requires trained clinical staff familiar with preparation and administration protocols. Manufacturer and professional society resources provide clinical education, as well as guidance on benefits verification and reimbursement processes to support adoption [67–69]. Ongoing safety monitoring is conducted through FDA post-market surveillance systems and professional registries such as the AGA FMT and gut microbial therapies registry [69,70]. These systems track reported adverse events and contribute to the long-term safety profile of microbiota-based therapeutics. Ethical considerations include obtaining informed consent for donor-derived products and providing transparent disclosure of associated risks. Access inequities are significant in low- and middle-income countries, where donor screening and cold-chain infrastructure are limited. Addressing these disparities will be essential for equitable adoption.

## 7. Comparative Effectiveness and Precision Medicine

To summarise, the relative efficacy, certainty of evidence, and clinical features of major microbiome-based therapies are summarised in Table 3.

**Table 3.** Comparative clinical outcomes across microbiome therapies.

| Therapy | Condition | Best-Supported Outcome | Effect vs. Control | Approx NNT | Evidence Quality | Key Notes |
|---|---|---|---|---|---|---|
| FMT | Recurrent CDI | Clinical cure/recurrence prevention | Substantially higher cure vs. antibiotics; high effectiveness in recurrent/refractory CDI | | Moderate (mixed RCT/obs.) | Strong benefit across studies, but heterogeneity precludes a single pooled "success %" [3]. |
| Multi-strain probiotics | UC maintenance | Maintenance of remission | Evidence uncertain; no robust pooled benefit | | Low–very low | Cochrane review could not confirm routine benefit for UC maintenance [12]. |
| Vowst (SER-109) | Recurrent CDI | Recurrence at 8 weeks | 12.4% vs. 39.8% recurrence (absolute ↓ 27.4%) | ~4 | High (Phase 3 RCT) | Oral capsules × 3 days; FDA-approved microbiota product [59]. |
| Rebyota (RBX2660) | Recurrent CDI | Treatment success at 8 weeks | 70.6% vs. 57.5% success (absolute ↑ 13.1%) | ~8 | High (integrated licensure analyses + RCTs) | Single-dose rectal administration; FDA-approved [58]. |
| Bifidobacterium-containing probiotics (adjunct) | *H. pylori* eradication | Eradication rate; adverse effects | Modest increase in eradication and reduced AEs (strain/regimen dependent) | | Low–moderate | Benefits are small and strain-specific; strongest data are mixed-probiotic or *S. boulardii* analyses [32–35]. |
| VSL#3 (multi-strain) | UC induction/maintenance | Clinical remission/maintenance | Signals of benefit in UC in some analyses; heterogeneity limits precision | | Low–moderate | Effect sizes vary by study; dosing/optimal use not firmly established [11]. |

This table summarises key outcomes from microbiome-based therapies where results are supported by cited clinical trials or systematic reviews. "Effect vs. control" shows the most relevant and reproducible figure from high-quality sources. Approximate numbers needed to treat (NNT) are calculated only where absolute risk reduction (ARR) can be derived from published percentages; otherwise, this field is left blank. Evidence quality reflects the certainty ratings in the cited systematic reviews or regulatory submissions, or is inferred from trial design strength (e.g., Phase 3 RCT = high). ↑ indicates an absolute increase in the proportion of patients achieving the primary outcome compared with control; ↓ indicates an absolute reduction in the proportion of patients experiencing the adverse outcome compared with control. Abbreviations: AE: adverse event; ARR: absolute risk reduction; CDI: Clostridium difficile infection; FDA: U.S. Food and Drug Administration; FMT: fecal microbiota transplantation; H. pylori: Helicobacter pylori; NNT: number needed to treat; obs.: observational studies; RCT: randomised controlled trial; UC: ulcerative colitis.

### *7.1. Patient Stratification Advances Personalized Approaches*

Microbiome profiling offers a path toward precision medicine by using baseline composition and diversity data to inform treatment selection. Evidence shows that certain baseline microbiome characteristics, including diversity measures, are associated with improved response to interventions, supporting a personalized approach to microbiome-targeted therapy [71]. In clinical practice, this could involve a workflow where patients provide stool samples for sequencing, profiles are compared with known response-associated patterns, and clinicians select the most suitable intervention accordingly. Follow-up profiling could track compositional changes to guide therapy adjustments. Predictive biomarkers are not yet validated and vary across populations. Combining these with AI-based models raises

significant ethical and data privacy concerns, necessitating safeguards and transparency prior to clinical integration. While conceptual frameworks exist, detailed stepwise protocols and EHR integration remain proposals rather than routine practice [71].

Host genetic variation also influences treatment outcomes. For example, PNPLA3 gene polymorphisms are associated with varying metabolic phenotypes in NAFLD, which may interact with microbiota-targeted strategies [72]. Evidence from functional gastrointestinal disorders also supports this approach, as microbiota-targeted therapies such as rifaximin have demonstrated clinical benefit in IBS [73]. Biomarker research is progressing toward the development of predictive and monitoring tools. In IBD, baseline bacterial composition and shifts in microbial metabolite profiles have been associated with therapeutic response, suggesting potential for integrating microbiome and metabolite data into treatment algorithms [74]. Population-specific considerations include tailoring approaches for paediatric patients, who may have different safety profiles; ensuring close monitoring in immunocompromised individuals; and recognising that geographic and lifestyle factors influence baseline microbiome composition [75]. The baseline microbiome composition varies across populations due to diet, lifestyle, and environmental exposures. These differences influence treatment response and limit the generalizability of trial results, highlighting the importance of geographic diversity in clinical research.

### *7.2. Long-Term Outcomes Support Sustained Benefits*

Durability data show sustained benefit over weeks to a few months. In a randomised trial, frozen and fresh FMT were non-inferior for recurrent *C. difficile* infection, with clinical resolution assessed over up to 13 weeks [76]. Longer-term follow-up comes mainly from cohort protocols rather than national registries; for example, a severe/complicated CDI protocol combining FMT with selected vancomycin reported high success but is not a registry and does not provide 10-year outcomes [77]. Risk–benefit considerations remain favourable in appropriately selected patients, but rare serious events can occur. A report of fatal aspiration pneumonia during FMT administration highlights the need for strict procedural safeguards; overall safety depends on careful screening and technique, and benefits include meaningful symptom improvement in recurrent CDI settings [78].

## 8. Future Directions and Clinical Implications

### *8.1. Technological Convergence Drives Innovation*

The convergence of artificial intelligence, synthetic biology, and precision medicine is accelerating the development of microbiome-focused therapeutics. Machine-learning approaches can analyse high-dimensional clinical and -omics data to support precision treatment strategies, aligning with broader AI-enabled decision support in medicine [79]. The manufacturing of defined microbial consortia is moving toward greater standardisation and quality control, and next-generation sequencing is routinely used in research settings for the longitudinal monitoring of therapeutic microbes and host responses [80]. In oncology, multiple studies demonstrated that the gut microbiome is associated with response to anti-PD-1 immunotherapy in melanoma, highlighting the potential for microbiome-informed strategies alongside existing treatments [81,82]. While these findings motivate the use of combination approaches, prospective interventional trials are still needed to determine whether adding microbiome-directed therapies improves efficacy or affects toxicity profiles [81,82].

### *8.2. Regulatory Evolution Supports Innovation*

International regulatory frameworks from both the FDA and the EMA offer models that can inform the development of novel microbiome therapeutics. While the EMA's

reflection paper on advanced therapy medicinal product (ATMP) classification [83] and the FDA's gene therapy guidance for rare diseases [84] are not specific to microbiome products, they illustrate approaches to defining product categories, establishing manufacturing standards, and setting safety monitoring expectations for novel biologics. Clear product classification, such as the FDA's Live Biotherapeutic Product designation, can facilitate consistent regulatory review processes. Expedited pathways, including the FDA's Breakthrough Therapy designation [85] and the EMA's PRIME (Priority Medicines) program [86], provide enhanced scientific and regulatory support for promising interventions. These frameworks employ a risk-based approach to strike a balance between innovation and patient safety, potentially offering adaptable models for microbiome-based products.

### *8.3. Market Expansion Drives Investment*

The global microbiome therapeutics market is projected to grow from approximately USD 300 million in 2021 to USD 3.2 billion by 2032, driven by increasing clinical validation, regulatory approvals, and commercial uptake [87]. Strategic collaborations between major pharmaceutical companies and microbiome-focused biotechnology firms are accelerating product development by combining clinical, manufacturing, and market expertise [88]. Public market activity continues to expand. For example, Microba Life Sciences' listing on the Australian Securities Exchange (ASX) underscored investor confidence, with the company citing an estimated global sector value of USD 4.89 billion [89]. In the private sector, microbiome-focused companies have attracted more than USD 1.6 billion in venture capital funding over a two-year period, reflecting sustained market interest despite ongoing clinical and regulatory hurdles [90]. The evolution of the patent landscape strongly shapes competitive dynamics. In the pharmaceutical industry, patenting and enforcement activities frequently increase following major product approvals as companies work to secure and extend market exclusivity [91]. Concurrently, intellectual property strategies such as tiered licensing, patent pools, and collaborative agreements can help balance the need for innovation incentives with broader access goals, particularly in global health contexts [92]. A consolidated summary of technological, regulatory, and market trends shaping the future of microbiome-targeted therapies is presented in Table 4.

**Table 4.** Future Directions and Clinical Implications for Microbiome-Targeted Therapies.

| Theme | Key Developments | Clinical/Commercial Implications | Evidence or Market Indicators | Limitations/Gaps |
|---|---|---|---|---|
| **Technological convergence** | AI + -omics integration for precision treatment selection (↑) [79] | Supports personalized microbiome therapy; aligns with AI-enabled decision-making in medicine | AI models analyse high-dimensional clinical & microbiome data; early success in oncology | Prospective validation needed; risk of overfitting in small datasets |
| | Standardisation of defined microbial consortia manufacturing (↑) [80] | Improves reproducibility, quality, and safety of therapeutics | GMP-aligned processes emerging; regulatory interest in consistency | High cost of compliance; technical complexity |
| | Longitudinal monitoring via next-generation sequencing (↑) [80] | Enables dynamic tracking of microbiome composition & host response | Used in research; potential in clinical follow-up | Cost, data interpretation challenges |
| | Gut microbiome linked to anti-PD-1 immunotherapy response in melanoma (↑) [81,82] | Potential for microbiome-informed combination oncology regimens | Multiple studies show associations; rationale for interventional trials | Causality unproven; effect on toxicity unclear |

**Table 4.** *Cont.*

| Theme | Key Developments | Clinical/Commercial Implications | Evidence or Market Indicators | Limitations/Gaps |
|---|---|---|---|---|
| **Regulatory evolution** | EMA ATMP reflection paper & FDA gene therapy guidance [83,84] | Provide frameworks for novel biologics, adaptable to microbiome products | Clarify product categories, manufacturing, and safety expectations | Not microbiome-specific; interpretation may vary |
| | FDA Live Biotherapeutic Product (LBP) designation | Streamlines regulatory classification and review | Recognised pathway for microbiome-based products | Requires detailed manufacturing and clinical data |
| | Expedited pathways: FDA Breakthrough Therapy & EMA PRIME (↑) [85,86] | Accelerate development of promising microbiome therapeutics | Offer enhanced scientific/regulatory support | Reserved for high-impact products; stringent entry criteria |
| **Market expansion** | Global market projected USD 300M (2021) → USD 3.2B (2032) (↑) [87] | Demonstrates rapid sector growth potential | CAGR driven by approvals, validation, and adoption | Projections depend on regulatory success |
| | Pharma–biotech strategic collaborations (↑) [88] | Accelerate product development through shared expertise | Examples in manufacturing scale-up and trial execution | Risk of dependency on single large partners |
| | Public market example: Microba Life Sciences IPO on ASX (↑) [89] | Signals investor confidence; sector valued at USD 4.89B | Increased visibility for microbiome companies | Market volatility risk |
| | Private market: >USD 1.6B VC funding in 2 years (↑) [90] | Sustained investor interest despite hurdles | Supports pipeline diversification | Funding concentrated in select markets |
| | Patent & IP strategies [91,92] | Secure market exclusivity post-approval; promote access via tiered licensing/pools | Shapes competitive landscape; encourages innovation | Tension between exclusivity & equitable access |

Abbreviation: ↑ = growth or positive development/trend. AI: artificial intelligence; ATMP: advanced therapy medicinal product; EMA: European Medicines Agency; FDA: United States Food and Drug Administration; GMP: Good Manufacturing Practice; IPO: initial public offering; LBP: Live Biotherapeutic Product; PD-1: programmed cell death protein 1; PRIME: Priority Medicines; USD: United States dollars; VC: venture capital.

## 9. Clinical Practice Recommendations

### *9.1. Evidence-Based Implementation Guidelines*

Clinical practice integration should follow evidence hierarchies. Fecal microbiota transplantation (FMT) is recommended for recurrent Clostridium difficile infection after appropriate antibiotic regimens, supported by systematic review and meta-analysis evidence [93,94]. Selected probiotic preparations have supportive evidence in certain gastrointestinal indications, but benefits are strain- and condition-specific rather than universal [95]. Patient selection should consider clinical severity, comorbidities, and contraindications. Cohort and trial data underlying FMT commonly exclude severely immunocompromised patients and highlight procedural risks, underscoring the need for careful screening and monitoring in higher-risk groups [94]. Treatment protocols should standardise dosing, route, and follow-up according to published trial methods. For probiotics, effectiveness is strain-specific; while some multi-strain combinations show benefit in particular settings, consistent superiority over single-strain products is not established across conditions [95]. Additional considerations apply to vulnerable populations. In pediatric patients, responses to microbiome-targeted therapies may differ from adults, and long-term safety data remain limited. In immunocompromised individuals, careful donor screening and close monitoring are essential, as the risk of infection remains a concern.

### *9.2. Safety Monitoring Frameworks*

Comprehensive safety monitoring for microbiome therapies should include pre-treatment screening, active surveillance during therapy, and long-term follow-up, reflecting practices used in published FMT cohorts and calls for standardised protocols [96–98]. Screening protocols and pathogen-detection methods are critical components of risk control in gut-microbiota-modulating interventions, given the potential for unintended microbial effects noted in broader microbiome literature [96]. Adverse-event tracking should capture both immediate and delayed complications using standardised documentation, with sustained follow-up to characterise durability and late events. Long-term observational data after colonoscopic FMT illustrate the feasibility and value of such surveillance [97]. Professional guidance urging standardisation of FMT procedures underscores the role of provider education in appropriate patient selection and complication recognition [98]. Risk mitigation should emphasise awareness of contraindications, clear response protocols for complications, and multidisciplinary input, alongside quality-assurance/standardisation efforts to ensure consistent implementation across centres, as advocated in proposals to formalise FMT practice [98].

## 10. Conclusions

Microbiome-targeted therapies have progressed from experimental use to validated treatments, with FDA-approved products demonstrating clear clinical benefits. The strongest evidence supports FMT for recurrent *C. difficile* infection, while strain-specific probiotics show benefits in selected gastrointestinal conditions. Emerging approaches—such as engineered bacteria, bacteriophage therapy, and metabolite-based interventions—signal the next wave of precision microbiome medicine. Implementation requires evidence-based patient selection, standardised protocols, and robust safety monitoring, while cost-effectiveness and operational barriers remain challenges. Key research priorities include standardizing FMT protocols, validating predictive biomarkers for therapy selection, and establishing long-term safety registries. Future work should also evaluate cost-effectiveness and ensure equitable access across health systems.

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## Abbreviations

The following abbreviations are used in this manuscript:

| | |
|---|---|
| AAC | Antibiotic-Associated Colitis |
| ACG | American College of Gastroenterology |

| | |
|---|---|
| ACS | American Chemical Society |
| AE | Adverse Event |
| AGA | American Gastroenterological Association |
| AI | Artificial Intelligence |
| ARR | Absolute Risk Reduction |
| ASX | Australian Securities Exchange |
| ATMP | Advanced Therapy Medicinal Product |
| CA | California |
| CBER | Center for Biologics Evaluation and Research |
| CD | Crohn's Disease |
| CDI | Clostridium difficile Infection |
| COVID-19 | Coronavirus Disease 2019 |
| CRISPR | Clustered Regularly Interspaced Short Palindromic Repeats |
| DOI | Digital Object Identifier |
| EHR | Electronic Health Record |
| EMA | European Medicines Agency |
| EMBASE | Excerpta Medica Database |
| FDA | Food and Drug Administration |
| FMT | Fecal Microbiota Transplantation |
| FXR | Farnesoid X Receptor |
| GI | Gastrointestinal |
| GMP | Good Manufacturing Practice |
| HBV | Hepatitis B Virus |
| IBD | Inflammatory Bowel Disease |
| IBS | Irritable Bowel Syndrome |
| ICER | Incremental Cost-Effectiveness Ratio |
| IDSA | Infectious Diseases Society of America |
| III | Phase III Clinical Trial |
| IPO | Initial Public Offering |
| ISAPP | International Scientific Association for Probiotics and Prebiotics |
| JAMA | Journal of the American Medical Association |
| JB | Journal of Bacteriology |
| LBP | Live Biotherapeutic Product |
| MA | Meta-Analysis |
| MCG | Microgram |
| MD | Doctor of Medicine |
| MIB | Microbiome |
| NAFLD | Non-Alcoholic Fatty Liver Disease |
| NASH | Non-Alcoholic Steatohepatitis |
| NNT | Number Needed to Treat |
| PD-1 | Programmed Death-1 |
| PHAGE | Bacteriophage |
| PMID | PubMed Identifier |
| PRIME | Priority Medicines |
| RCT | Randomized Controlled Trial |
| RNA | Ribonucleic Acid |
| SER-109 | Microbiome Therapeutic Product SER-109 |
| SHEA | Society for Healthcare Epidemiology of America |
| SSIEM | Society for the Study of Inborn Errors of Metabolism |
| UC | Ulcerative Colitis |
| US | United States |
| USD | United States Dollar |
| VC | Venture Capital |

| | |
|---|---|
| VOWST | Microbiome Therapeutic Product Vowst |
| VSL | Probiotic Formulation VSL#3 |

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