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REVIEW

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Gut microbiome therapy: fecal microbiota transplantation vs live biotherapeutic products

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ABSTRACT

The human intestine hosts a complex ecosystem of various microorganisms, collectively known as the gut microbiome, which significantly impacts human health. Disruptions in the gut microbiome are linked to various disorders, including gastrointestinal diseases, such as *Clostridioides difficile* infection and inflammatory bowel disease, as well as metabolic, neurological, oncologic conditions. Fecal microbiota transplantation (FMT) and live biotherapeutic products (LBPs) have emerged as prospective therapeutic procedures to restore microbial and metabolic balance in the gut. This review assesses the latest advancements, challenges, and therapeutic efficacy of FMT and LBPs, highlighting the need for standardization, safety, and long-term evaluation to optimize their clinical application.

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The gut microbiome and its innovative therapeutic roles

The human intestine, a complex organ, harbors trillions of microorganisms, including bacteria, viruses, archaea, fungi, and protozoa, as well as their bioactive products.[1] The Human Microbiome Project refers to the collective genomes of these entities as the 'gut microbiome'.[2] The gut microbiome is established at birth and shaped by factors such as breastfeeding and delivery methods during the first decade of life.[3] It undergoes significant changes during childhood, achieving highly diverse that stabilizes in adulthood.[4] However, its composition remains influenced by numerous factors, including chronological age, geography, and lifestyle.[5]

Homeostasis in the gut microbiome refers to a stable yet adaptable balance that responds to internal and external changes to maintain overall health. This intricate microbial community can be influenced by various factors, including diet and medications, rendering it susceptible to disturbances in homeostasis. These disturbances result in compositional and functional perturbations, potentially leading to adverse health outcomes termed dysbiosis.[6] It is crucial to note that not all changes in gut microbial communities equate to dysbiosis or negative health impacts, and causality is often difficult to establish. Dysbiosis can be induced by various approaches, including drugs, changes in nutrient supply, and the immune system.[7] This may trigger a cascade of dysbiotic conditions within the intestinal milieu, leading to the proliferation and dispersal of antibiotic-resistant genes in the gut microbiota.[8] Dysbiosis has been associated with the pathogenesis and progression of numerous diseases, not only in the gastrointestinal (GI) tract, such as *Clostridioides difficile* infection (CDI) and inflammatory bowel disease (IBD),[9] but also in other regions of the body, including the liver and brain.[10,11] While differences in the gut microbiota are observed between patients with and without certain diseases, it is often unclear whether these changes cause the disease or are a consequence of it. Further research is needed to establish causality.

Strategies are therefore needed to modulate or substitute indigenous organisms instead of completely

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eradicating them. Fecal microbiota transplantation (FMT) and live biotherapeutic products (LBPs) are modalities that may be used to modulate and/or replace endogenous microbiota. Their mechanisms of action, however, differ markedly.[12] FMT involves transferring not only fecal-associated microbial communities but also microbe-derived metabolites, such as short-chain fatty acids (SCFAs) and bile acids, along with other resident microorganisms like phages, archaea, and fungi.[13] In contrast, LBPs offer a more targeted approach, using specific bacterial strains or consortia identified through preclinical studies.[14] LBPs have been defined by the U.S. Food and Drug Administration (FDA) as biological products that i) contain live organisms, such as bacteria and yeast, ii) are intended for the prevention, treatment, or cure of a human disease or condition, and iii) are not vaccine.[15]

Fecal microbiota transplantation

In FMT, the entire microbial community is transferred from the screened feces of healthy donors to a recipient to rectify dysbiosis in the gut. Since its initial use in 1958,[16] FMT has been shown to be a reliable treatment for recurrent CDI and may have potential to treat other diseases.

The initial step of FMT consists of a rigorous donor selection process based on certain inclusion criteria, including age 18 to 50 years; no history of or risk factors for underlying symptomatic medical conditions or ailments, such as fever or gastrointestinal disturbances, or any other diseases that can impact gut microbiota; and lack of treatment with antimicrobials (antibiotics, antivirals, antifungals) or probiotics within the 6 months prior to donation.[17] Subsequently, the fecal matter from selected donors is screened to determine its suitability for administration.[18] These steps in FMT are essential for minimizing the risk of transmitting infectious agents and other harmful substances to the recipient, ensuring the health and balance of the donor microbiome, preventing adverse reactions in recipients, and complying with regulatory standards. Through this comprehensive screening process, the therapeutic benefits of FMT can be maximized. Simultaneously, the clinical conditions of the recipient are thoroughly assessed. One factor that must be considered is antibiotic treatment for the recipient, along with the duration and necessity of treatments; however, it is clear that antibiotics should be stopped 12–48 hours before fecal infusion.[19] The final step in the FMT process, involves the determination of the state of the fecal matter, whether fresh or frozen; and the selection of the optimal site and frequency of administration.[18,20]

Although the U.S. Food and Drug Administration approved FMT as an investigational new drug in 2013, its widespread clinical implementation remains limited, primarily due to ongoing research on its effectiveness and safety. Standardized protocols and U.S. Food and Drug Administration guidelines are still lacking, mainly due to the inherent diversity of FMT samples and challenges in controlling product quality.[21] Therefore, the complex nature of FMT necessitates careful consideration and periodic updates to administration guidelines (Box 1, 2).

Live biotherapeutic products

Reconstruction of the gut microbiome with designed bacteria, whether single or multiple, can offer feasible and targeted advantages, comparing the generalness of FMT. LBPs drive innovative approaches and advancements in the medical sciences, thereby fostering extension in the pharmaceutical sector. In 2019, the European Pharmacopoeia has expanded the definition of 'LBPs' to describe "medicinal products composed of live microorganisms (bacteria or yeasts) intended for human administration," further specifying the potential routes of administration, including oral and vaginal, as well as various pharmaceutical formulations.[32]

The development of LBPs began with a thorough investigation of the microbiome profiles of individuals with diseases, as these microbiomes differ from those of healthy individuals. Comparative analyses can identify constituents that are depleted or enhanced in various diseased states. Once potential candidates for treatment have been identified, *in vitro* experiments are required to determine the functional capabilities and safety profiles of the candidate microbiota. Subsequent *in vivo* experiments in animal models can determine the therapeutic potential and mechanisms of action of these microbe-derived compounds.

Box 1 :Vaginal microbiota transplantation

The vaginal microbiota consist of a diverse and complex community of microorganisms that includes Lactobacillus species. Based on taxonomic analysis from extensive sampling using vaginal swabs, the vaginal microbiota of most reproductive-age women can be classified into five community state types (CSTs).[22] Four of these CSTs are dominated by single species, with CST I, CST II, CST III, and CST V being dominated by Lactobacillus crispatus, Lactobacillus gasseri, Lactobacillus iners and Lactobacillus jensenii, respectively. By contrast, CST IV is composed of various facultative and obligate anaerobes, including Gardnerella, Atopobium, Prevotella, Candidatus Lachnocurva vaginae, Sneathia, Peptoniphilus, Finegoldia and Megasphaera.[23] Vaginal microbiota play a critical role in maintaining vaginal health and preventing infection by pathogens. A shift in the composition of the vaginal microbiota from predominantly lactobacilli-dominated to diverse polymicrobes can lead to recurrent urinary tract infections and gynecological diseases such as bacterial vaginosis (BV), vulvovaginal candidiasis and pelvic inflammatory diseases.[24] BV is a prevalent vaginal infection caused by an imbalance in the vaginal microbiota. Although BV has been treated with various agents, including antibiotics, single vaginal probiotics, and estrogen therapy, these interventions have been ineffective in treating recurrent BV.[23] Vaginal microbiome transplantation (VMT), which involves transferring a sample of vaginal fluid from a healthy donor to a recipient with an imbalance or disruption in the vaginal microbiota, has shown promise in the treatment of intractable BV. The objective of VMT is the restoration of the Lactobacillus domination of the recipient's vaginal microbiota, thereby inhibiting the growth of pathogenic bacteria and alleviating symptoms.[23] VMT in five women with intractable BV reduced BV symptoms in all five, although three required multiple VMTs, including a change in donor. No adverse effects were reported during the 21-month follow-up period, with the transplanted microbiota remaining stable in four recipients for up to 21 months.[25] Treatment of BV with synthetic bacterial consortia transplantation, consisting of lactic acid-producing bacteria, showed that synthetic bacterial consortia transplantation significantly attenuated BV, but was less effective than VMT in murine models.[26] Although VMT has shown promising results, additional studies in large patient cohorts are needed to determine the safety and efficacy of this procedure and to develop guidelines for the collection, processing, and administration of vaginal microbiota transplants.

Box 2: Fecal Virome Transplantation

Viruses residing in the gut are collectively known as the "gut virome". The number of viruses living in the gut is typically reported as virus-like particles, with an estimated 109 virus-like particles per gram of feces. Most of the viruses in the gut virome are bacterial viruses, known as bacteriophages, with the remainder being archaeal and eukaryotic viruses. The gut virome has been associated with human diseases, with virome compositions in healthy individuals differing from those in patients with CDI,[27] IBD,[28] and colorectal cancer.[29] Although the mechanisms by which the virome affects diseases have not yet been determined, some animal model studies have consistently revealed potential mechanisms. For example, virus-like particle recognition by host toll-like receptors 3 and 7 reduced disease severity in mice with DSS-induced colitis.[30] Furthermore, genetic variations in toll-like receptor 3 and 7 altered disease severity in patients with IBD, suggesting that the enteric virome directly affects the disease through the host immune system. Because the gut virome is important, its contribution during FMT must be evaluated. Some members of the gut virome were reported to be transferred from donor to recipient during FMT.[27] In addition, changes in the gut virome of FMT recipients are associated with clinical outcomes,[27,29] indicating that viruses transmitted through FMT are actively involved, not simply passive bystanders. FMT treatment of patients with CDI significantly reduced the abundance of Caudoviricetes, which accounts for most of the gut virome.The effects of fecal virome transplantation were also assessed following the transfer of cecal virus-like particles from lean donor mice into obese recipient mice.[31] Fecal virome transplantation led to a significant loss of weight and improvement of glucose intolerance in the recipient mice, indicating the potential of fecal virome transplantation as a therapeutic approach.

Ultimately, LBPs are classified as medicinal products and are therefore regulated similarly to other biological medicines, requiring their quality, safety, and efficacy to be thoroughly assessed and produced by Good Manufacturing Practice prior to receiving marketing authorization[33] (Figure 1). However, the regulation and standardization of LBPs vary significantly across countries. In the US, many commercial probiotics, a form of LBPs, are marketed as dietary supplements and are not subject to the rigorous testing required for drugs. This can result in variability in quality and efficacy.

FMT and LBPs in diverse pathologies

Clostridioides difficile infection

Clostridioides difficile is an anaerobic, Gram-positive bacterium that is a leading causative agent of CDI. It can cause colon infection, with symptoms ranging from mild diarrhea to severe CDI, which can include kidney failure and a swollen abdomen, to life-threatening conditions, including colonic perforation, toxic megacolon, and death.[34] Although antibiotic treatment is the primary first-line therapeutic intervention for CDI, the estimated rate of first recurrence, attributable to antibiotic use, is about 20%.[35] Because antibiotic use itself is a factor significantly contributing to recurrent CDI (rCDI), FMT may be a promising therapeutic approach for rCDI. Indeed, the success rate of FMT of one or multiple infusions for rCDI is almost 100%.[36]

Several mechanisms underpin the efficacy of microbiome-based treatments for rCDI, such as restoring microbial ecology,[37] altering microbe-derived metabolites,[38] and competitively excluding pathogens through colonization resistance.[39] The

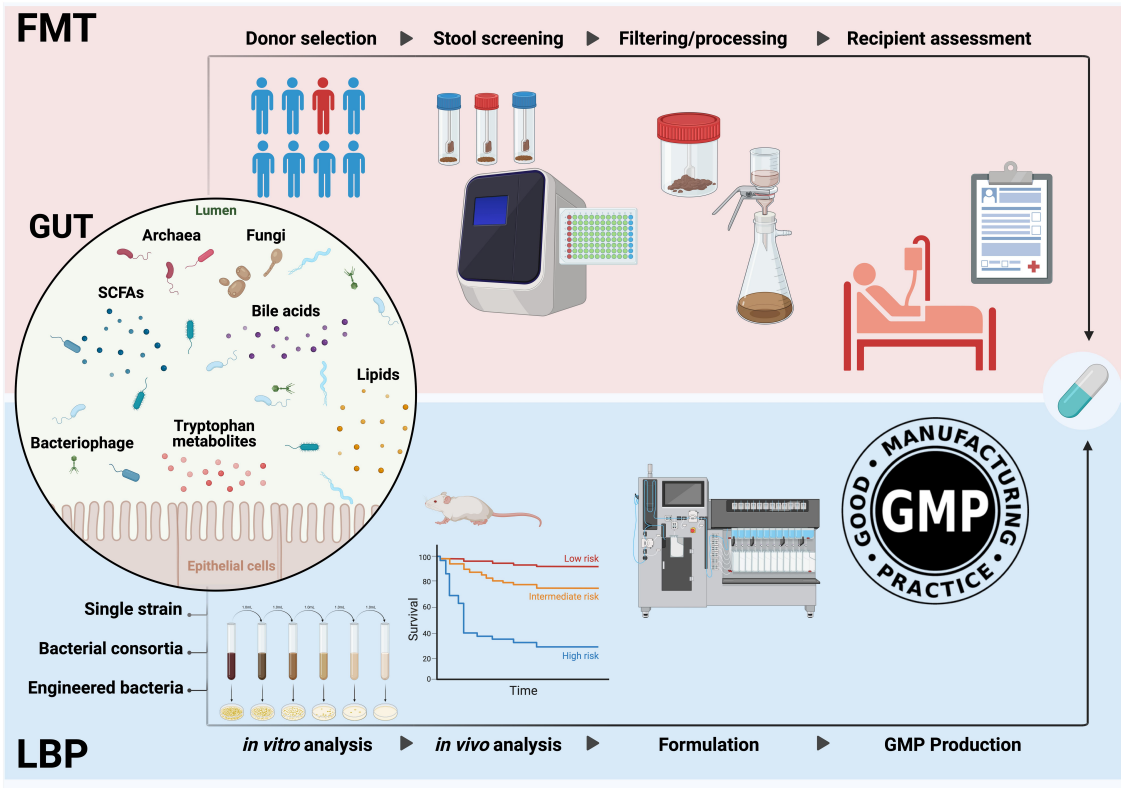

Figure 1. The process of the production of FMT and LBPs. Created in BioRender. Kim, D. (2023) BioRender.com/o29o880

fecal microbiota introduced through microbiome-based therapies play a pivotal role in modulating both the microbial community and microbial diversity within the GI milieu. In addition, these introduced microbiota ferment dietary components, yielding microbe-derived metabolites, such as SCFAs and bile acids, which alter the gut environment in a manner less conducive to *C. difficile* proliferation. SCFAs are microbe-derived metabolic by-products resulting from the fermentation of dietary fibers, with acetate, propionate, and butyrate being the most prevalent constituents.[40] SCFAs have anti-inflammatory and immunomodulatory properties, thereby contributing significantly to immune homeostasis. Investigations into the properties by which SCFAs protect against *C. difficile* involve an exploration of their potential mechanisms in stabilizing the intestinal epithelial barrier during CDI and their interaction with innate immune responses.[41] For example, FMT was reported to significantly alter the production of SCFAs in the recipient gut, increasing SCFA levels.[37] LBPs may have similar mechanisms of action, as supplementation with well-defined bacterial strains has been shown to significantly elevate the levels of SCFAs.[42] In addition, bile acids profoundly influence metabolic regulation in the host, with empirical evidence showing a linkage between *C. difficile* and bile acid levels in the large intestine.[43] Concentrations of primary bile acids in the stool were reported to be significantly higher in individuals with CDI than in healthy persons, although levels of secondary bile acids in the stool were undetectable in the former.[44] Microbe-derived secondary bile acids have been found to inhibit *C. difficile* growth, whereas higher levels of primary bile acids enhance *C. difficile* spore germination and proliferation.[45] Consequently, manipulating and restoring bile acid homeostasis within the intestinal milieu may be promising in the prevention and/or treatment of CDI. General metabolomics and targeted bile acid analyses showed that FMT contributed to the normalization of metabolite composition and the correction of abnormal bile acid metabolism. Harmoniously balanced indigenous microbiota can effectively compete with

pathogenic microbes by occupying strategic ecological niches and utilizing available resources, thereby effectively preventing pathogen proliferation.[39] Additional research is required to further determine these intricate mechanisms, enhancing comprehension of the therapeutic efficacy of FMT against rCDI (Tables 1 and 2).

Combinations of bile acids with *Clostridium scindens* may synergistically inhibit *C. difficile* growth *in vivo*. *C. scindens* transforms primary bile acids into secondary bile acids, enhancing resistance to *C. difficile* colonization.[88] Human microbiota-based therapies now undergoing clinical trials include CP101 (Finch Therapeutics), an undefined live biotherapeutic oral capsule that includes the lyophilized feces of healthy donors;[104] VE303 (Vedanta Biosciences), a combination of eight clonal human commensal bacterial strains chosen for their capacity to confer resistance to *C. difficile* colonization;[46] and Ser-109, now known as live-brpk (Seres Therapeutics), an experimental oral microbiome therapy comprised of live, refined Bacillota (formerly Firmicutes) bacterial spores.[89] Furthermore, RBX2660, now known as live-jslm (Rebiotix Inc.), a commercially prepared microbiota-based live biotherapeutic containing a minimum of 10^7/mL live diverse organisms such as Bacteroidota and Bacillota, has emerged as a new option to reconstruct dysbiosis caused by CDI.[90]

Inflammatory bowel disease

IBD is a set of chronic inflammatory disorders of the GI tract, with its primary subtypes being ulcerative colitis (UC) and Crohn's disease (CD). Although distinct in clinical presentation, these conditions share common features, including chronic inflammation, disease relapse, and a substantial impact on patients' quality of life. UC predominantly affects the colon and rectum, leading to continuous inflammation and ulceration of the mucosal lining, with sites of inflammation limited to the innermost lining of the colon. By contrast, CD can affect any part of the GI tract, from the mouth to the rectum, and is characterized by transmural inflammation.[105] The gut microbiota are crucial in the pathogenesis of IBD, with significant differences in the composition of the gut microbiome between IBD patients and healthy individuals. These differences include alterations in microbial diversity, abundance, and the balance between beneficial and pathogenic microorganisms.[106]

Conventional treatments for UC utilize pharmacological agents, such as 5-aminosalicylates and sulfasalazine, to reduce inflammation, but these treatments are associated with high rates of adverse effects, including flatulence, abdominal pain, and GI disorders. Moreover, the percentage of patients maintaining remission is generally lower.[107] Consequently, microbiome-based therapeutic interventions, such as FMT and LBPs, were introduced to increase remission rates. These interventions can influence the host's immune system by orchestrating innate and adaptive immunity, including antigen-presenting cells and T cells.[108] These treatments can also influence the host's GI milieu by enhancing the integrity of the mucosal barrier. This enhancement involves several concerted actions, including the reduction of epithelial cell apoptosis, the enhancement of the composition of the mucus layer, the upregulation of expression of tight junction proteins, and subsequent reductions in intestinal permeability and associated inflammatory responses.[109] Dysregulation of bile acid metabolism has been implicated in the pathogenesis of IBD. Targeting this bile acid-gut microbiota axis may therefore attenuate inflammatory processes and ameliorate the clinical symptoms of IBD.[110]

A randomized, double-blind clinical trial compared autologous FMT with pooled FMT, both involving the administration via colonoscopy of anaerobically prepared frozen stool, in 73 patients with mild-to-moderate UC. The remission rate at 8 weeks was found to be significantly higher in patients treated with pooled than autologous FMT for 1 week.[111] In addition, the clinical remission rate was found to be substantially higher in 31 patients who underwent FMT with a fresh fecal slurry from a single donor via colonoscopy than in 30 patients administered a placebo infusion.[47] The etiology of CD remains unclear. A study of 17 patients who had achieved clinical remission following oral corticosteroid treatment and subsequently underwent FMT using frozen stool from a single donor via colonoscopy found that the

Table 1. Clinical applications of FMTs on diseases.

		FMT			
Diseases		Total number of patients who received FMT	Number of donors	Administration route	References
Gastrointestinal diseases	CDI	10	1 and a stool bank	gastroscope	38
		49	2	oral	46
	IBD	38	pooled	colonoscopy	47
		30	single	colonoscopy	48
		8	single	colonoscopy	49
		174	multiple	colonoscopy	50
	IBS	44	stool bank	oral capsule	51
		165	single	gastroscopy	52
Liver diseases	PSC with IBD	10	single	colonoscopy	53
	PSC (BC)	1	single	endoscopy	54
	SAH	51	unknown	nasoduodenal tube	55
		60	single	nasoduodenal tube	56
	MASLD	75	multiple	colonoscopy	57
	Hepatic encephalopathy	20	single	enema	58
		10	single	upper endoscopy, flexible sigmoidoscopy, and oral capsules	59
		36	unknown	unknown	60
Metabolic diseases	T2D	17	multiple	transendoscopic enteral tubing	61
		40	6	unknown	62
	Metabolic syndrome	34	4	oral capsules	63
		11	single	oral capsules	64
		38	multiple	nasoduodenal tube	65
		9	single	gastroscopy	66
		10	4	oral capsules	67
Neurological diseases	ASD	40	multiple	oral or colonoscopy	68
		24	single	colonoscopy and gastroscopy	69
		9	multiple	oral capsules and enema	70
		18	5	oral capsules and enema	71
	PD	1	single	transendoscopic enteral tubing	72
	Epilepsy	1	single	gastroscopy	73
	Tourette Syndrome	1	single	gastroscopy	74
Autoimmune diseases	MS	9	multiple	rectal enema	75
		1	multiple	rectal catheter	76
		1	single	rectal enema	77
	RA	1	single	colonoscopy	78
	Systemic lupus erythematosus	20	7	oral capsules	79
	Celiac disease	1	single	nasoduodenal tube	80
	T1D	11	7	nasoduodenal tube	81
	GVHD	21	single	unknown	82
		1	single	endoscopy	83
		23	single	nasojejunal or gastric tube	84
		7	7	endoscopy, nasogastric tube, and oral capsules	85
Oncological disorder	Immunotherapy	10	2	oral and colonoscopy	86
		15	multiple	colonoscopy	87

*Abbreviations: CDI – Clostridioides difficile infection; IBD – inflammatory bowel disease; IBS – irritable bowel syndrome; PSC – Primary sclerosing cholangitis; BC – bacterial cholangitis; SAH – Severe alcoholic hepatitis; MASLD – Metabolic dysfunction-associated steatotic liver disease; T2D – Type 2 diabetes; ASD – autism spectrum disorders; PD – Parkinson's disease; MS – Multiple sclerosis; RA – Rheumatoid arthritis; T1D – Type 1 diabetes; GVHD – Graft-versus-host disease.

steroid-free clinical remission rates at 10 and 24 weeks were 87.5% and 50.0%, respectively, in the FMT group, and 44.4% and 33.3%, respectively, in the sham transplantation group.[48] Another study, including 174 patients with CD, evaluated the effects of FMT administered via various routes, including endoscopy, nasojejunal tube, and mid-gut transendoscopic enteral tubing. Before transplantation, 79.9% (139/174), 83.9% (146/174), and 11.5% (20/174) of these patients exhibited abdominal pain, diarrhea, and steroid dependence, respectively. Following FMT, the total score of target symptoms associated with CD decreased gradually and significantly.[49] Nevertheless, FMT for IBD does not consistently yield positive outcomes.[50]

Two general mechanisms are involved in the treatment of IBD with LBPs, with LBPs either: enhancing anti-inflammatory responses or impeding pro-inflammatory responses. These approaches aim to rebalance the composition of the gut microbiota and enhance immune tolerance within the

Table 2. LBPs on diseases.

	LBP			
Diseases	Methods	Bacterial strains	Single or consortium	References
CDI	In vitro	*Lacticaseibacillus rhamnosus* R0011, *Lactobacillus helveticus* R0052, *Saccharomyces boulardii* CNCM I-1079, and *Bifidobacterium longum* R0175	single	43
	Human	Strains from *Saccharomyces*, *Lactobacilli*, *Bifidobacteria*, and *Streptococci*	consortium	88
	Human	VE303 strain 01 (or VE303-01); *Enter- ocloster bolteae*, VE303-02; *Anaerotruncus colihominis*, VE303- 03; *Sellimonas intestinalis*, VE303-04; *Clostridium symbiosum*, VE303-05; *Blautia* sp001304935, VE303-06; *Dorea longicatena*, VE303-07; *Longicatena innocuum*, and VE303-08; *Flavonifractor* sp000508885	consortium	46
	Human	Purified Firmicutes spores	consortium	89
	Human	Strains from Bacteroidetes and Firmicutes	consortium	90
IBD	Human	*E. coli* Nissle 1917	single	91
	Human	*E. coli* Nissle 1917	single	92
	Human	Strain from *Bacteroides thetaiotaomicron*	single	93
	Mouse	17 strains from *Clostridium* clusters IV, XIVa, and XVIII	consortium	94
	Mouse	*Candidatus Arthromitus*, *Clostridium celatum*, *Clostridiales* bacterium VE202-01, and *Bifidobacterium pseudolongum* strain PV8-2	consortium	95
Obesity/MetS	Human	two strains of *Streptococcus thermophilus*, two strains of *Lactobacillus acidophilus*, one strain of *Lactobacillus rhamnosus*, and one strain of *Enterococcus faecium*	consortium	96
T2D	Mouse	Strain from *Akkermansia* spp.	single	97
ASD	Mouse	*Blautia stercoris* MRx0006	single	98
	Mosue	*Parabacteroides goldsteinii* MTS01	single	99
AD	Mouse and human	Strain from *Lactiplantibacillus plantarum*	single	100
PD	Mouse	Strain from *Clostridium butyricum*	single	101
Immunotherapy	Human	Including *Clostridium butyricum*	consortium	102
	Mouse	Strains from four *Clostridiales* bacteria	consortium	103

*Abbreviations: CDI – Clostridioides difficile infection; IBD – inflammatory bowel disease; T2D – Type 2 diabetes; ASD – autism spectrum disorders; AD – Alzheimer's disease; PD – Parkinson's disease.

gut.[112] Although LBPs have shown promise in treating IBD in preclinical studies, no LBPs have yet been approved for IBD treatment by regulatory authorities. One notable example is *Escherichia coli* Nissle 1917 (EcN), which was originally not classified as an LBP but was utilized as one of the first "live probiotic strains" for IBD. Several randomized controlled trials have demonstrated the effectiveness of EcN, including its equivalence to mesalamine in maintaining remission in UC patients.[91] Mutaflor®, a microbial drug containing lyophilized EcN as an active component, is another noteworthy development.[92] Additionally, *Bacteroides thetaiotaomicron* (Thetanix®; 4D Pharma), a single-strain LBP that antagonizes the transcription factor nuclear factor kappa B and has been found to reduce tumor necrosis factor-alpha and other pro-inflammatory cytokines, is undergoing clinical trials.[93] Furthermore, a combination of 17 strains of *Clostridia*, isolated from human gut commensals, was found to enhance the abundance of $CD4^+FoxP3^+$ regulatory T cells, inducing anti-inflammatory responses, and to inhibit dextran sodium sulfate (DSS)-induced inflammation in germ-free (GF) mice.[94,95] Bioscience companies, such as Vedanta Biosciences and Seres Therapeutics, have developed rationally designed bacterial combinations that are candidates for treating IBD. For example, a phase I trial of VE202 (Vedanta), which consists of human indigenous microbiota strains, was recently completed in patients with UC (NCT05370885/ClinicalTrials.gov). In addition, SER-287 (Seres), which consists of a combination of Bacillota spores, may be a potential treatment for patients with active mild-to-moderate UC; however, a phase 2 trial of SER-287 was recently terminated due to a lack of clinical efficacy (NCT03759041/ClinicalTrials.gov) (Box 3).

Metabolic disorders

Numerous chronic metabolic disorders, including obesity, metabolic syndrome, type 2 diabetes (T2D), Metabolic dysfunction-associated steatotic liver disease (MASLD, formerly NAFLD), and Metabolic dysfunction-associated steatohepatitis (MASH, formerly NASH), are linked to abnormalities in gut microbiota composition and microbial-derived metabolites.[120] The World Health Organization (WHO) has defined obesity as a body mass index (BMI) > 30 kg/m^2, although this threshold may differ among nations.[121]

Box 3. Engineered LBPs

Engineered Live Biotherapeutic Products (eLBPs) are defined as genetically tailored microorganisms, precisely modified for designated diagnostic or therapeutic functions within a clinical context.[113] Microbiome engineering methodologies may have therapeutic properties, particularly in diseases that remain refractory to existing treatment modalities.[114] Engineered EcN strains may act as potential eLBPs in metabolic disorders and cancers. For example, SYNB1618 (Synlogic) was developed to treat phenylketonuria through phenylalanine degradation. Phenylketonuria is a hereditary metabolic disorder that results in a genetic defect in the enzyme phenylalanine hydroxylase. SYNB1618 has been found to reduce blood phenylalanine concentrations and inhibit increases in serum phenylalanine after an oral phenylalanine administration in mice and primates.[115] Lactic acid bacteria, notably Lactococcus lactis, may act as an engineered biotherapeutic, especially in the treatment of IBD. Strains of L. lactis genetically engineered to secrete the anti-inflammatory cytokine interleukin-10 were found to mitigate inflammation in murine models of DSS-induced colitis.[116] Several bacterial species with pathogenic potential, such as Listeria monocytogenes and Salmonella subspecies, possess the intrinsic ability to infiltrate and colonize neoplastic tissues. Strains with attenuated virulence have been engineered, with these eLBPs directed against of oncological targets. Many clinical trials are testing the efficacy and safety of these innovative eLBPs as novel anti-cancer agents.[117] Despite obstacles to the advances of eLBPs, including safety considerations[118] and manufacturing difficulties,[119] these agents continue to demonstrate promising results, suggesting their potential in contemporary medical therapeutics.

Obesity increases vulnerability to a range of comorbidities, particularly metabolic syndrome, cardiovascular disorders, T2D, and liver diseases such as MASLD and MASH.

The composition of the microbiome differs in individuals with and without obesity and metabolic syndrome. The microbiome in individuals with obesity and metabolic syndrome is characterized by significant reductions in several microbial taxa, including *Akkermansia*, *Faecalibacterium*, *Oscillibacter*, and *Alistipes*.[122] Furthermore, elevated levels of *Limosilactobacillus reuteri* have been linked to comorbidities in mice with western diet-induced obesity[123] and obese individuals, contributing to substantial weight gain.[124] By contrast, *Bifidobacterium animalis*, *Methanobrevibacter smithii*, and various *Lactobacillus* species are more abundant in normal weight individuals, with *M. smithii* levels being lower in obese than in normal weight individuals.[125] Obesity is also distinguished by an elevated prevalence of the class *Bacilli* and its associated families, *Streptococcaceae* and *Lactobacillaceae*, along with significant reductions in the abundance of several taxonomic groups within the class *Clostridia*.[126] These changes in microbial composition have been associated with comorbidities related to obesity. Bioactive molecules produced by gut microbiota, such as SCFAs and proteins, also have beneficial effects on host metabolism.[127,128] Two large-scale metagenome studies have analyzed the features of the gut microbiota in individuals with T2D, finding that the abundance of opportunistic pathogens was enriched.[129] Notable perturbations in gut microbiota of *Proteus* and *Enterobacter* and decreases in the abundances of *Ruminococcus* and *Lactobacillus*.[130,131]

FMT and LBPs hold substantial potential as treatments for metabolic diseases, with data extrapolated from animal models providing an initial indication of their efficacy. Studies in GF mice administered a high-fat diet or a conventional diet have shown that microbial diversity and composition can affect the metabolic and immunological functions of subjects with metabolic disorders. Depending on their gut microbiomes, both hyperglycemic and hypoglycemic patterns have been observed in mice with the same genotype and similar dietary patterns.[132] GF mice weighed less and had lower amounts of white adipose tissue than conventional mice even when calorie intake in the former was increased following the administration of the high-fat diet.[133] GF mice with a chow diet who received FMT from mice with diet-induced obesity demonstrated a greater weight gain and higher white adipose tissue levels than GF mice who received FMT from lean donor mice.[134] Similar results were observed when FMT from obese humans was administered to GF recipients.[135] FMT has also shown benefits in a preclinical model of T2D, Black and Tan, Obese Tufted (BTBR) mice, including lower weight gain, reduced albuminuria and tumor necrosis factor-alpha levels, and ameliorated insulin resistance.[136] FMT treatment for 8 weeks was found effective in attenuating high-fat diet-induced steatohepatitis in mice.[137] Cohousing experiments involving healthy wild-type mice and mice predisposed to MASH development due to genetic alterations in the inflammasome pathway, found that the exchange

of microbiota through coprophagia resulted in the induction of liver steatosis and inflammation in previously healthy mice.[138] Moreover, a non-blinded, one-armed intervention trial of FMT from healthy donors evaluated the reconstitution of the gut microbiota in 17 patients with T2D, finding that the T2D symptoms significantly improved symptoms in 11 patients after 12 weeks of FMT treatment.[61] Transplants of high alcohol *Klebsiella pneumoniae*, isolated from the feces of individuals with MASH, have been observed in 60% of patients with MASLD and have the ability to induce MASLD in mice.[139] A randomized, controlled clinical trial of FMT in patients with MASLD found that FMT was associated with partial improvements in the symptoms of MASH, including amelioration of fat accumulation in the liver and abnormal small intestinal permeability.[57] Other studies have reported limited improvements, whereas most studies have found that markers of obesity and metabolic syndrome were not significantly altered in patients with these diseases.[63]

Strains of *Enterococcus faecium* and *Streptococcus thermophilus* significantly reduced serum concentrations of low-density lipoprotein cholesterol levels and increase levels of fibrinogen in overweight and obese subjects who were administered yogurt fermented with two strains of *S. thermophilus* and one strain of *E. faecium*.[96] *Akkermansia muciniphila* has the potential to enhance lipid and insulin concentrations, glucose metabolism, and intestinal permeability.[140] Modifying the gut microbiota, such as increasing *Akkermansia* spp., can ameliorate glucose tolerance and attenuate adipose tissue inflammation.[97]

Neurological disorders

The gut communicates bidirectionally with the brain via neural, immune, endocrine, and metabolic pathways, collectively known as the gut-brain axis.[141] This complex network, involving intricate molecular and functional interplay between the gut and brain,[141] is implicated in many diseases, including autism spectrum disorder (ASD), Alzheimer's disease (AD), and Parkinson's disease (PD). Microbial dysbiosis may increase intestinal permeability, resulting in mucosal inflammation, with toll-like receptors being involved in the onset and progression of neurological disorders. The stimulation of toll-like receptors within microglia, the intrinsic immune cells of the central nervous system, induces the synthesis of pro-inflammatory cytokines and chemokines, thereby intensifying neuroinflammation.[142]

ASD, a group of neurodevelopmental disorders resulting in behavioral manifestations, is often accompanied by GI dysfunction, such as increased susceptibility to intestinal inflammation and altered gut permeability. An open-label trial assessing the impact of FMT on GI and neurobehavioral symptoms in 40 children diagnosed with ASD found that FMT alleviated both GI and neurobehavioral symptoms without severe adverse effects.[68] ASD management may also include innovative biotherapeutics. For example, the novel MRx0006 strain of *Blautia stercoris* was found to ameliorate pathophysiological symptoms associated with ASD, including deficits in social interactions, repetitive behaviors, and anxiety-like traits, in the BTBR *T+ Itpr3tf/J* mouse model of autism.[98] Furthermore, another potential LBP strain, *Parabacteroides goldsteinii* MTS01, mitigated anxiety-like behaviors, social deficits, and intestinal inflammation in offspring of female model mice with an immune activated ASD-like condition.[99]

AD, a progressive neurological disorder in which amyloid-beta and hyperphosphorylated tau proteins accumulate in the brain, may also be associated with the human gut microbiome.[143] According to the "microbiota-neuroinflammation connection" hypothesis of AD, perturbations in the gut microbiota composition can potentially drive the progression of AD.[144] Dysregulation of the gut microbiota may trigger intestinal inflammation, setting off a cascade of systemic inflammation. This systemic inflammation may exacerbate neuroinflammation and increase the permeability of the blood-brain barrier, allowing harmful substances such as lipopolysaccharides to enter the brain. These detrimental substances may contribute to neuroinflammation, one of the hallmark features of AD.[144] The gut microbiota composition in transgenic mice with an AD-like pathology characterized by amyloid and neurofibrillary tangles ($ADLP^{APT}$) was found to differ significantly from the gut microbiota composition in healthy wild-type mice. These microbial alterations were

associated with intestinal and systemic immunological irregularities mediated by gut bacteria. Importantly, FMT demonstrated significantly reduced the deposition of amyloid-beta plaques and neurofibrillary tangles, as well as ameliorating memory impairment, in ADLP^{APT} mice.[145]

To date, no LBP interventions have been approved to treat AD, although supplementation with *Lactiplantibacillus plantarum* has shown potential by modulating cortisol synthesis within the hypothalamic-pituitary-adrenal axis, inhibiting the kynurenine route in tryptophan catabolism, reducing chronic inflammatory processes, enhancing dopamine and serotonin concentrations and the synthesis of SCFAs, and reducing serum concentrations of pro-inflammatory cytokines, corticosterone, and lipopolysaccharides, as well as markers of inflammation such as soluble fractalkine, and CD163.[100]

PD, the second most prevalent neurodegenerative disorder worldwide, is characterized by progressive impairment in voluntary motor control.[146] Notably, some gut-related symptoms, primarily constipation, manifest as prodromal indicators years before the onset of motor symptoms.[147] The composition of the gut microbiota differs in PD patients and healthy individuals. A case report described a PD patient who experienced severe constipation and leg tremors, both of which were notably attenuated 1 week after FMT treatment.[72] Nevertheless, the effectiveness of FMT in patients with human PD cases requires further investigation. *Clostridium butyricum* treatment of mice with PD induced by injection of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine was found to ameliorate motor deficits, synaptic dysfunction, and microglial activation, as well as to attenuate loss of dopaminergic neurons.[101] Two gut bacterial strains, *Parabacteroides distasonis* MRx0005 and *Megasphaera massiliensis* MRx0029, were found to have anti-inflammatory and antioxidant activities *in vitro*, reducing the release of pro-inflammatory cytokines by glioblastoma and astrocytoma cells. These cytoprotective properties suggest that these strains may be suitable LBP candidates for neurodegenerative diseases such as PD.[148]

Cancer

Microbiome communities may be associated with the development, metastases, and treatment response of various cancer. Beyond *Helicobacter pylori*,[149] several bacterial species, including *Fusobacterium nucleatum*, *Escherichia coli*, *Bacteroides fragilis*, and *Salmonella enterica*, have been detected within tumor tissues or implicated in tumor formation and metastasis.[150–153] In addition to the impact of single bacterial species, dysbiosis may be associated with susceptibility to cancer development.[154] Studies are evaluating the mechanisms underlying the effects of the intestinal microbiome on cancer, including distance-dependent, distance-independent, and immunological mechanisms.[153,155,156]

Although immunotherapy, such as treatment with immune checkpoint inhibitors (ICIs), has revolutionized the treatment of various types of cancer, response rates are extremely low.[157] Modulating the gut microbiome by FMT and LBPs may improve the efficacy of antitumor treatments, such as chemotherapy, immunotherapy, and radiotherapy.[158,159] Indeed, the microbial immunomodulatory reaction can affect the efficacy of and responses to immunotherapy, as well as the occurrence of subsequent immune-related adverse events, such as colitis in patients treated with monoclonal antibodies against cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) and pneumonitis in patients treated with monoclonal antibodies against programmed cell death protein-1/programmed death-ligand 1 (PD-1/PD-L1).[160] A combination of anti-PD-1 therapy and FMT from responder donors has exhibited efficacy.[86] Moreover, genomic, molecular, and microbial biomarkers associated with response to ICI have been identified.[161] Responders have shown that increases in the abundances of *Bifidobacterium longum*, *Collinsella aerofaciens*, and *F. prausnitzii* were associated with increases in anti-PD-1 response and CD8+ T cell activation, and reductions in myeloid cells expressing interleukin-8.[87] Transferring the fecal matter of patients into mice with GF mice with tumor induction or mice treated with antibiotics and ICI improved the efficacy of immunotherapy.[162] Transfer of FMT from

"responder" patients, who showed a favorable response to ICI, into similar model mice demonstrated that ICI responsiveness could be transferred to recipient mice. By contrast, FMT from "non-responder" patients into the same mice did not affect responsiveness to ICI.[163,164] Clinical trials in humans suggested that FMT from ICI responders could transfer responsiveness to ICI-resistant patients with melanoma.[86,87]

The *C. butyricum* strain MIYAIRI 588 has been shown effective in ameliorating the dysbiosis associated with gastrointestinal pathology and in significantly increasing the overall survival of patients with small-cell lung cancer.[102] In addition to single probiotic strains having a promising role, combinations of bacteria consortia could modulate environmental homeostasis more efficiently. *Clostridiales* in the gut commensal microbiota was associated with a lower tumor burden in murine models of colorectal cancer and was significantly lower in colorectal cancer patients than in healthy individuals. A combination of four strains of *Clostridiales* strains (CC4; *Roseburia intestinalis*, *Eubacterium hallii*, *F. prausnitzii*, and *Anaerostipes caccae*) orally administrated to mice resulted in the complete cure of colorectal cancer.[103]

Challenges underlying gut microbiome-based therapy

Donor selection in FMT; defining 'healthy' human gut microbiota

Optimizing donor selection is crucial for FMT to prevent adverse events associated with the donated fecal materials.[20,165] The 2016 European Consensus Conference recommended thorough screening, including repeated blood and stool tests, and a general questionnaire focused on the medical history and lifestyle habits of the donor, based on exclusion criteria suggested by the European Commission for the selection of allogeneic living donors of human tissue transplants.[20,166] Similar criteria have also been recommended by the French National Guidelines of FMT for the treatment of rCDI.[167]

Because FMT involves the transfer of the gut microbiota from healthy individuals, it is necessary to define a 'healthy' gut microbiome. High-throughput sequencing technologies have shown that the phyla Bacteroidota, Bacillota, and Actinomycetota are abundant in the healthy microbiome,[168] although minor variations in this ecosystem have been reported, with these variations due to population and geographic differences. In addition to its composition, the richness and diversity of the gut microbiota may serve as determinants of a healthy gut profile.[169] The associations between dysbiosis-related disorders and distinct microbial profiles can allow the determination of a healthy microbiome, along with a population-based evaluation of the microbial community and intensive, personalized health monitoring.

Lack of standardization in pharmacy

Two significant concerns in FMT preparation are the route of administration and the condition of the feces. Combined oral and rectal transfer was compared with exclusively rectal transfer of donor feces to preterm neonate pigs to determine differences in bacterial colonization patterns. Bacteria in the stomach and colon were identified by 16S rRNA gene amplicon sequencing. Both oral and rectal transfer of FMT were found to increase the relative abundance of the genera *Bacteroides* and *Prevotella* and to reduce the relative abundance of *Enterococcus* in the colon.[170] However, oral and colonoscopic FMT could not be directly compared in humans, suggesting the need for additional studies testing the effects of route of administration on efficacy.

Moreover, it is essential to determine whether the feces should be administered fresh or after freezing and thawing. A comparison showed that the use of frozen instead of fresh FMT did not result in a lower proportion of patients with clinical resolution of diarrhea.[171] By contrast, another study reported that the freezing protocol significantly altered the cultivable bacterial community and the viability of the bacterial cells, with most selected biodiversity indices being slightly lower for frozen samples.[172] Issues regarding the processing and manufacturing of LBPs have also arisen, including whether these agents should be administered as capsules or

powders, as well as their optimal composition[173] and those which have a risk of contamination and poor labeling are possible in markets without proper regulation.[174,175]

Donor strain engraftment

The stability of donor-derived strains engraftment is a key consideration for both FMT and LBPs. While recipients with higher engraftment levels of donor strains tend to have better clinical outcomes,[176] the relationship between donor strain colonization, recipient strains resilience, and clinical success requires further investigation.[177] In addition, the most effective dosages and frequencies of FMT and LBPs must be determined. Both FMT and LBPs face challenges related to the frequency of treatment administration.[178,179] Furthermore, the primary safety issue associated with LBPs was the decrease in colonization due to the absence of certain components, such as metabolites and viruses, as these absences could result in a lack of systematic cooperation.

Pre-treatment with antibiotics

It remains unclear whether pre-treatment with antibiotics can affect the efficacy of FMT. Pre-treatment involves the administration of antibiotics to the recipient to reduce the microbial population residing in the GI tract. The primary objective of this pre-treatment is to create a favorable environment in the recipient's gut that reduces resistance to colonization, thus promoting the successful engraftment of the introduced donor microbiota and minimizing competition from native microbial populations.[180] Pre-treatment, however, may also potentially facilitate the colonization and proliferation of bacteria with antibiotic-resistance genes.[181]

Existing consensus and established clinical guidelines[19,182] suggest that a minimum pre-treatment period with antibiotics can mitigate any potential adverse effects that antimicrobial agents may exert on the FMT material and its subsequent efficacy. However, the precise antibiotic pre-treatment protocol necessitates a case-specific approach, contingent upon the particular clinical context. Decisions regarding antibiotic pre-treatment should be based on the unique circumstances of each FMT recipient.

Safety issues

Safety concerns could impede the commercialization of FMT and LBPs. The primary safety issue for FMT is the risk of transmitting infectious agents, including bacteria, viruses, and parasites, from donors to recipients.[183] Although donors are screened for contagious diseases, there is still a risk of transmission, as donor-derived infections may be asymptomatic or undetected by current screening methods.[20] In June 2019, U.S. Food and Drug Administration published a safety alert following one fatality and one invasive infection, both due to extended-spectrum beta-lactamase-producing *Escherichia coli*, following FMTs derived from a single donor.[183,184] Similarly, six patients were found to be infected with enteropathogenic *E. coli* or Shiga toxin-producing *E. coli* subsequent to the investigational administration of FMT, with this transmission thought to arise from the materials obtained from several donors in the U.S. that were employed to create FMT products. Two fatalities after FMT were reported in patients with pre-existing chronic health conditions, but the effects of infections on these deaths remain uncertain.[185]

The administration of FMT or LBPs can result in unintended alterations in the microbiome, and the administration of FMT can result in the introduction of pathogenic bacteria or antibiotic-resistance genes.[186] All these alterations can have adverse effects on the health of the host. These safety concerns can be mitigated by establishing stringent safety protocols and regulations for FMT and LBPs. These should include thorough donor screening and testing for infectious agents, as well as the monitoring of recipients for adverse events and unanticipated microbiome alterations. The development of standardized manufacturing processes and quality control can enhance the safety and efficacy of these therapies. Future studies should include long-term longitudinal follow-up, enabling a more comprehensive understanding of the temporal dynamics and enduring effects associated with related FMT and LBPs (Figure 2).

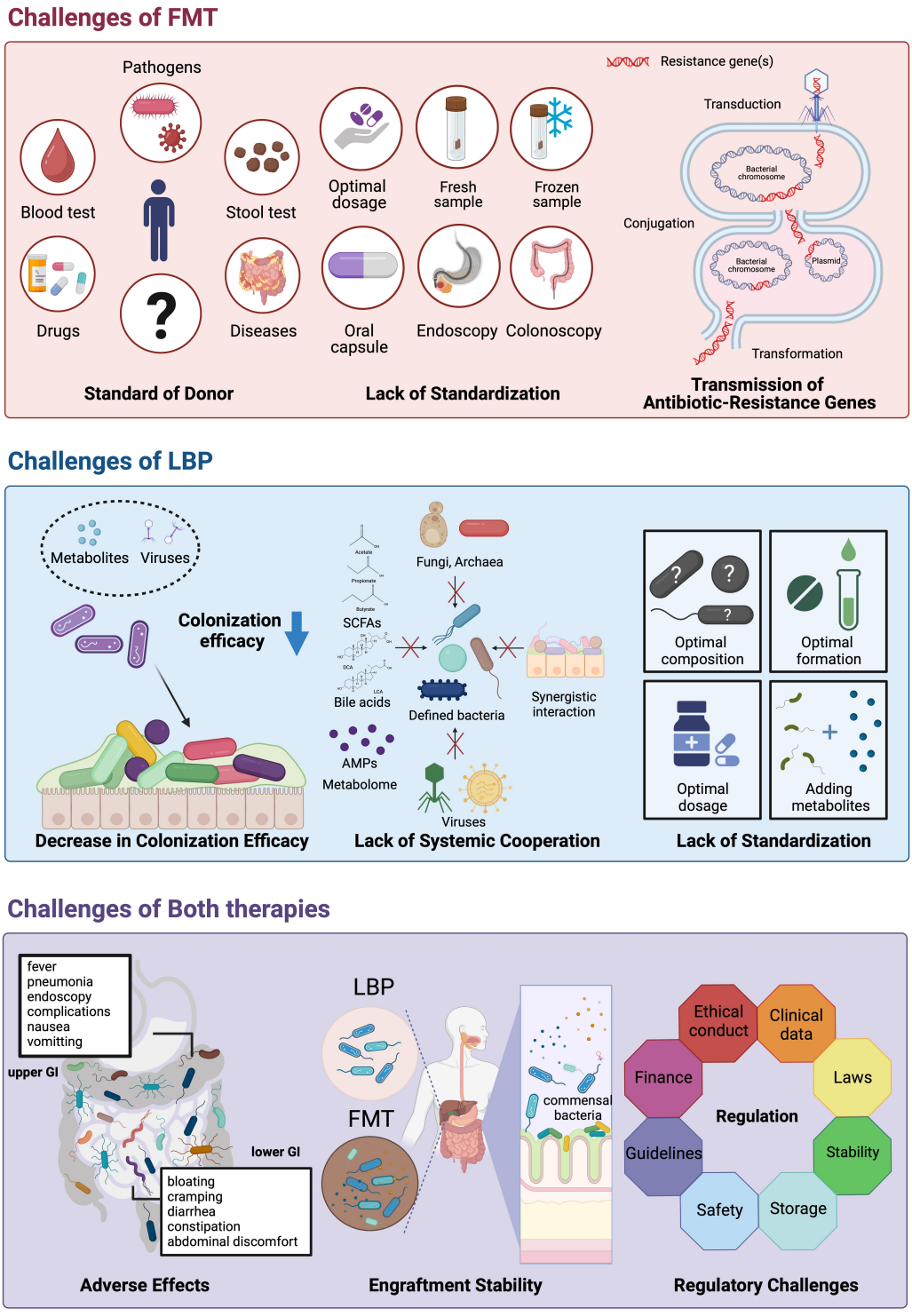

Figure 2. Challenges of FMT, LBP, and both therapies. Created in BioRender. Kim, D. (2023) BioRender.com/k92z535

Conclusions

In conclusion, manipulating the gut microbiome through FMT and LBPs can significantly enhance the management of various pathologies. While these treatments have demonstrated empirical effectiveness in clinical settings, challenges remain, including the need for procedural standardization, comprehensive safety profiles, and long-term efficacy assessments. FMT has proven effective in treating rCDI and shows

promise for IBD and other metabolic and neurological disorders by restoring gut microbiota balance. Conversely, LBPs offer a more refined therapeutic approach with the potential for customized probiotic formulations. Well-designed clinical trials with long-term follow-up are essential to validate the therapeutic benefits of these microbiome-focused interventions, overcoming the limitations of conventional treatments.

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