CORA Cork Open Research Archive
Cartlann Taighde Oscailte Chorcaí

Title	Not just passengers: Phages as agents of genetic exchange in fecal microbiota transplantation
Authors	Gonzalez Pastor, Belén;Shkoporov, Andrey;Hill, Colin
Publication date	2026-05-13
Original Citation	Gonzalez Pastor, B, Shkoporov, A & Hill, C 2026, 'Not just passengers: Phages as agents of genetic exchange in fecal microbiota transplantation', Cell Host and Microbe, vol. 34, no. 5, pp. 780-789. https://doi.org/10.1016/j.chom.2026.03.017
Type of publication	Article (peer-reviewed)
Link to publisher's version	https://www.scopus.com/pages/publications/105038431338 - 10.1016/j.chom.2026.03.017https://www.scopus.com/pages/publications/105038431338?origin=resultslist
Rights	Publisher Copyright: © 2026 The Authors. - https://creativecommons.org/licenses/by/4.0/
Download date	2026-10-31 16:34:38
Item downloaded from	https://hdl.handle.net/10468/18846

UCC
University College Cork, Ireland
Coláiste na hOllscoile Corcaigh

CellPress
OPEN ACCESS

Cell Host & Microbe

Perspective

Not just passengers: Phages as agents of genetic exchange in fecal microbiota transplantation

Belen Gonzalez Pastor,[1] Andrey N. Shkoporov,[1] and Colin Hill[1,*]
[1]APC Microbiome Ireland, School of Microbiology & Department of Medicine, University College Cork, Western Road, Cork, County Cork T12 YT20, Ireland
*Correspondence: c.hill@ucc.ie
https://doi.org/10.1016/j.chom.2026.03.017

SUMMARY

Fecal microbiota transplantation (FMT) is an effective therapy for recurrent *Clostridioides difficile* infection and is increasingly being explored for other microbiota-associated diseases. However, general research has largely focused on bacterial engraftment, overlooking the contribution of the gut virome. In this perspective, we highlight phage-mediated horizontal gene transfer (HGT) as a potentially influential process occurring following FMT. Donor-derived phages may potentially influence community structure, engraft in resident bacteria, and modulate microbial functions or host physiology. In addition, temperate phages are well-equipped to mobilize bacterial genes, such as metabolic functions, stress-response traits, and antibiotic resistance determinants, raising the possibility that gene flow could well contribute to FMT outcomes. We propose a conceptual model in which phages act as bidirectional mediators of adaptation, not only accompanying bacterial communities but also influencing gut ecosystems in subtle, yet potentially consequential, ways.

INTRODUCTION: FRAMING THE FORGOTTEN PASSENGER

The human gut harbors one of the most densely populated and genetically diverse microbial ecosystems in nature.[1] This dynamic environment is inhabited not only by bacteria but also by archaea, fungi, parasites, and a diverse array of viruses. These viruses are dominated by bacteriophages (phages) that infect bacterial hosts with high specificity.[2] Phages can influence bacterial population dynamics by regulating bacterial growth, promoting strain turnover, and modulating microbial community resilience through cycles of infection, lysogeny, and bacterial lysis.[3,4] However, as noted recently,[5] while phages clearly influence strain-level dynamics, their long-term impact on overall community composition at the species level and above may be limited and context dependent. Rather than restructuring whole communities at higher taxonomic levels, phages may modulate the diversity and evolutionary trajectories of individual bacterial populations.

In healthy individuals, microbial community structures are stabilized by a complex network of ecological and biochemical interactions among individual community members, the human host, and the abiotic environment.[6,7] Phages contribute to ecosystem stability, diversity, and functionality by exerting strong selective pressures on microbial phenotypes and mediating horizontal gene transfer (HGT). Phage-driven HGT between bacterial cells comprises both erroneous packaging and delivery of (random) host DNA fragments and delivery of genes contained directly within temperate phage genomes, which affect bacterial phenotypes during lysogeny. This process allows bacteria to rapidly acquire new traits and adapt to changing conditions.[8–10]

This state of relative ecological equilibrium, resulting from a complex web of host-microbe, microbe-microbe, and phage-microbe interactions, provides numerous benefits to the human host. These include colonization resistance against pathogens and pathobionts, a stable supply of physiologically relevant short-chain fatty acids, synthesis of essential vitamins, and the modulation of immune responses.[7,11–13]

However, when this equilibrium is disrupted by factors such as changes in diet, exposure to antibiotics, infections, or disease, the resulting microbial imbalance can have significant consequences. A clear example is recurrent *Clostridioides difficile* infection (rCDI), where antibiotic-induced community perturbations reduce colonization resistance, allowing rapid expansion of *C. difficile*. This increase in pathogen abundance leads to a sharp increase in pathogen numbers and the subsequent production of toxins that cause epithelial damage and inflammation, further exacerbating microbial imbalance and creating a vicious cycle of chronic inflammation.[14] Altered community structures have also been associated with conditions such as inflammatory bowel disease (IBD) and metabolic disorders.[15,16]

Fecal microbiota transplantation (FMT) is a clinical procedure in which fecal material from a healthy donor is transferred into the gastrointestinal tract of another individual in an attempt to re-establish a balanced gut microbial community (Figure 1). FMT has proven efficacy in treating rCDI and is under investigation for a range of other conditions, including IBD and metabolic syndrome.[17–19] However, while the FMT research and practice has largely focused on bacterial engraftment and the functional restoration of the microbial community, the transplanted fecal material contains much more than just bacterial cells. Among

 © 2026 The Authors. Published by Elsevier Inc.
This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

CellPress
OPEN ACCESS

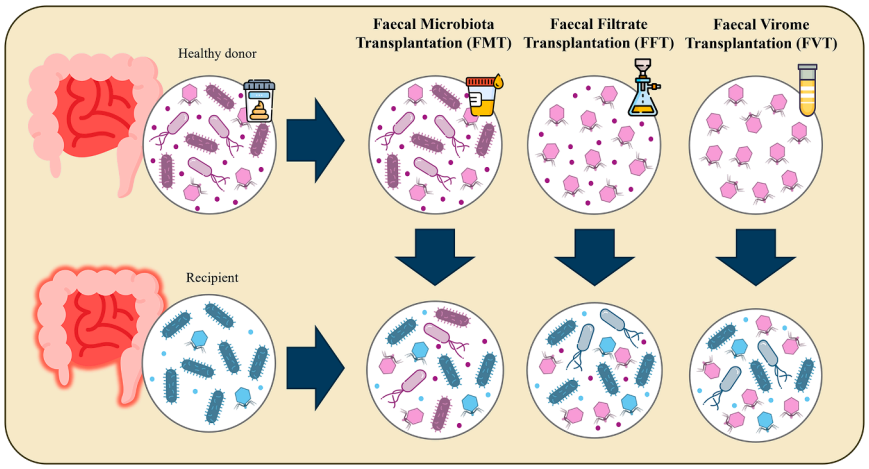


Figure 1. Schematic overview of FMT, FFT, and FVT

Representation of the different donor-derived preparations and the material delivered to the recipient. A healthy donor microbiota (pink) serves as the source material. In fecal microbiota transplantation (FMT), resuspended donor stool with minimal processing is administered, resulting in the transfer of donor bacteria, phages, and metabolites to the recipient microbiota (blue). In fecal filtrate transfer (FFT), the resuspended stool is filtered to remove intact bacterial cells, hence only phages and metabolites reach the recipient microbiota. In fecal virome transplantation (FVT), the filtrate undergoes further purification to enrich for the viral fraction, leading to the transfer of phages only. The intended outcome in all cases is the restoration of a healthy gut microbial ecosystem.

the overlooked components of FMT are phages, which are inevitably transferred along with their bacterial hosts.[20,21]

Phages represent a significant and highly dynamic component of the gut microbiome, and it has been shown that donor phages can engraft long-term in FMT recipients. For instance, stable engraftment of donor-derived phages was observed in recipients who responded successfully to FMT, persisting for up to 12 months.[21] This suggests a lasting, donor-specific shift in the gut virome after FMT, likely reflecting long-term changes in bacterial composition due to the narrow, strain-specific host range of phages. However, despite their abundance and persistence, the role of phages in shaping the post-FMT microbiota or in influencing clinical outcomes remains underexplored.

The human gut is increasingly recognized as a hotspot for HGT, since the prevailing dense microbial populations and environmental pressures create optimal conditions for genetic exchange.[22] Phages, particularly those capable of lysogeny and transduction, are active mediators of HGT and can facilitate the dissemination of genes that confer fitness advantages to their bacterial hosts, such as antibiotic resistance, enhanced virulence, phage defense, antimicrobial activity, and improved metabolic capacities.[10,23–26] Recent research has characterized the evolutionary dynamics of microbial communities in the gut, demonstrating that phages can contribute to rapid adaptive changes via HGT. A recent report[27] showed that prophage transfer between *E. coli* strains in the mouse gut confers significant selective advantages to invading lineages, allowing lysogenization to outpace mutation as a driver of adaptation. Further support comes from single-molecule nanopore sequencing of virus-like particles, which revealed that up to 5% of capsid-packaged DNA in the human gut virome is bacterial in origin, providing direct evidence of widespread phage packaging of bacterial DNA across diverse gut taxa.[28]

These findings collectively suggest that phage-mediated HGT is a potentially significant driver of genome plasticity and evolution within the gut microbial community and thus underscores the need to re-evaluate the role of phages in FMT. Should phages be regarded as passive passengers, merely hitching a ride with their bacterial hosts, or are they active drivers of gene exchange capable of reshaping recipient microbiomes after FMT? In this perspective, we discuss one of the least investigated roles of phages in FMT: their ability to facilitate rapid HGT and thereby act as active contributors rather than passive elements.

THE GUT VIROME: ROLE OF PHAGES IN BACTERIAL ECOLOGY

Among the diverse community of microorganisms coexisting in the human gut, phages are the most abundant viral entities and play a key role in shaping the gut microbial landscape.[9,29] Gut phages display long-term persistence, with fecal viromes showing high individuality and temporal consistency. This stable structure appears to be maintained by a small number of highly prevalent viral genomes that form strong associations with specific bacterial genera, such as *Bacteroides* and *Faecalibacterium*.[4] Recent evidence further indicates that, once established, up to 80% of viral sequences are detectable over time and that virome composition closely mirrors that of the bacterial community.[30] Typical bacterial cell densities in the human gut reach 10^{11}–10^{12} cells per gram of intestinal content, whereas virus-like particles (VLPs) are estimated at 10^{8}–10^{9} particles per gram, corresponding to a virus-to-bacterium ratio of 0.01–0.1.[9,31]

Phages usually follow either a temperate or lytic cycle. In the lytic cycle, a phage infects a host cell, hijacks the bacterial machinery to produce new viral particles, and ultimately causes the host cell to lyse, releasing newly synthesized phages. In contrast, temperate phages can enter the lysogenic cycle, where their genetic material integrates into the host genome and remains dormant as a prophage.[32] This dormant state can persist until certain environmental cues trigger the prophage to reactivate and transition to the lytic cycle.[33]

Studies of the human gut microbiome reveal a high density of phage genomes but comparatively few phage particles, with an estimated ratio of phage particles to genomes between 1:100 and 1:10, pointing to a dominance of temperate phages in this environment. The low abundance of free phage particles suggests that most phages are present as prophages rather than actively engaging in lytic replication. This low induction rate suggests both a minimal fitness cost to bacterial hosts and an evolutionary advantage in having integrated phages,

Table 1. Ecological models of stable phage–host coexistence

Model	Description	References
Kill-the-Winner (KtW)	Phages are more likely to infect the most abundant bacterial hosts. This prevents any single species from dominating and maintains diversity, since resistance to infection comes with metabolic costs	[5]
King-of-the-Mountain (KoM)	At high host densities, phage resistance increases as a result of horizontal gene transfer and mutations. This reduces phage replication and creates a positive frequency-dependent pattern, where more abundant hosts are also more resistant to infection	[5]
Piggyback-the-Winner (PtW)	During periods of rapid bacterial growth, temperate phages integrate into host genomes and replicate in tandem. When host densities peak, phages switch to the lytic cycle, so their infection mode is linked to ecological conditions	[5]
Arms-Race Dynamics (ARD)	Bacteria and phages co-evolve in a stepwise way, with hosts gaining resistance and phages evolving counter-resistance. This leads to genetic escalation and nested infection networks	[41]
Fluctuating-Selection Dynamics (FSD)	Host genotypes switch back and forth between resistant and infective, driven by selection and the costs of resistance. This helps maintain diversity over time	[41]

such as immunity against infection by related phages or access to genes that may confer adaptive traits. Together, these advantages promote long-term coexistence and may enhance the evolutionary fitness of bacterial hosts in the complex gut ecosystem.[31,34]

Although temperate phages appear to dominate the gut virome, lytic phages also play a role in microbial community structure and dynamics. For instance, Reyes and colleagues[35] demonstrated that phage predation in the gut occurs in a sequential manner, with different phages targeting specific bacterial hosts at distinct times, leading to the rise of resistance through ecological and epigenetic mechanisms rather than fixed mutations. Similarly, Shkoporov and colleagues[4] showed that interactions between lytic crAss-like phages and *Bacteroides intestinalis* promote long-term coexistence via phase variation, with phages maintaining bacterial phenotypic diversity without exerting strong lytic pressure. Moreover, Wilde and colleagues[36] reported that reintroducing virulent phages into synthetic gut communities had minimal effects on overall microbial composition and metabolism, suggesting that lytic phages exert localized rather than community-wide disruptions.

However, the ecological role of lytic phages should not be underestimated. Recent evidence complicates the traditional view of lytic phages as simply suppressors of bacterial numbers. Castledine and colleagues[37] showed that phage-resistant *Variovorax* clones, isolated from evolved populations and cultured in the absence of phage, reached higher bacterial densities during the death phase compared with susceptible clones. This demonstrates that the resistance-associated genetic change altered the host's growth dynamics in a stable, heritable way rather than as a transient response to phage presence.

Beyond their canonical role in impacting the abundance of bacterial species (Table 1), phages can also modulate microbiota diversity and composition at the subspecies and strain level and influence metabolic output and functional interactions within the gut ecosystem. The temperate phage BV01 alters gene expression in its host, the common gut bacterium *Phocaeicola vulgatus*, by integrating into the bacterium's genome and disrupting the promoter region of a gene encoding a tryptophan-rich sensory protein (TspO). This disruption leads to the repression of bile acid deconjugation and impacts the metabolism of bile acids.[38] In murine models, phage targeting of defined community members induced broad knock-on effects on metabolism, including shifts in neurotransmitter levels and bile acid metabolism.[39] Extending these findings, *in vitro* phage predation over a simplified human microbiome consortium led to significant shifts in non-target microbial populations and metabolic output. These effects were less pronounced *in vivo* but still associated with improved host outcomes such as reduced inflammation.[40] Together, these studies highlight that phages can exert major effects on sub-species diversity, functionality, and host-microbiota interactions, despite having a limited impact on the overall taxonomic composition of gut communities at the species level.

Building on these observations, the close association and absolute dependence of phages on their bacterial hosts means that phage transfer during FMT is inevitable. How these transferred phages affect microbial interactions, community structure, and functional outcomes in the recipient gut remains an important and open question.

PHAGE TRANSFER IN FMT: EVIDENCE AND OPEN QUESTIONS

While FMT dynamics have traditionally focused on the bacterial component of the fecal material, recent clinical and preclinical studies provide strong evidence that donor phages engraft in FMT recipients and remain stable over time, modifying the gut virome in ways that may influence host health.[21,42]

Engraftment of donor microbes has been found to positively correlate with the α-diversity of the donor phageome, suggesting that richer and more diverse phage communities may enhance FMT success.[20] This observation aligns with the widely known ecological principle that diversity confers resilience and adaptability—a principle often applied to bacterial ecosystems but less explored in the context of viromes.[43]

CellPress
OPEN ACCESS

Consistent with this view, donor phage diversity has been linked to improved clinical resolution of rCDI. As observed recently,[44] patients receiving FMT from donors with higher phage α-diversity had better outcomes, characterized by reductions in Gammaproteobacteria and restoration of Clostridia. These findings suggest that phages may help shape bacterial community dynamics after FMT, either by suppressing overrepresented taxa or by promoting colonization. Such changes may not only reflect compositional restructuring but may also suggest functional shifts in microbial metabolism. A subsequent study[45] found that patients with better clinical outcomes possessed phage communities that clustered more closely with those of healthy donors. Furthermore, the study identified specific phage groups whose presence was associated with improved clinical outcomes, suggesting a potential role in treatment success. Previously, increased *Caudoviricetes* richness in donor samples had been identified as a predictor of FMT success in rCDI.[46] Given that *Caudoviricetes* encompasses a broad range of temperate phages, this raises the possibility that lysogenic conversion or phage-mediated HGT may contribute to long-term remodeling of the gut microbiome. Taken together, these findings may indicate a role for phages in both microbial modulation and disease resolution.

Collectively, these studies confirm that donor phages not only transfer but can stably engraft in recipients, reshaping the gut virome in rCDI patients. However, the functional implications of these changes remain unclear.

A major challenge in interpreting these findings is the tight coupling between phage and bacterial strain dynamics, as changes in phage populations often mirror shifts in their bacterial hosts. As a result, many FMT studies remain inherently correlational, making it difficult to assign causality to phages independently of bacterial engraftment. However, a subset of experimental approaches involving cell-free virome transfer provides stronger evidence that phages can be directly involved in modulating microbial community structure and function, beyond serving as passive correlates of their bacterial hosts.

Fecal virome transplantation (FVT) is a cell-free microbiome-based therapeutic strategy aimed at harnessing the therapeutic potential of the virome (Figure 1). In a mouse model of diet-induced obesity, FVT containing all viruses from the donor, both bacteriophages and eukaryotic viruses, showed variable but generally positive effects, such as reduced liver pathology and altered immune responses. In the same study, a modified virome preparation (FVT-ChP), where eukaryotic viruses were removed or inactivated while bacteriophages were preserved, significantly improved glucose clearance. Virome preparations modified by other treatments, however, did not show clear metabolic benefits.[47] This suggests that intact viromes may be more effective than depleted ones under certain conditions, highlighting a key conceptual issue: while depleted viromes offer greater safety and precision, they may lack the ecological coherence and complexity inherent to intact viral communities. Meanwhile, Rasmussen and colleagues[48] reported on a murine model in which FVT from lean donors reduced weight gain and normalized blood glucose parameters in diet-induced obese mice, effectively shifting their phenotype toward that of lean controls. More recently, this group[49] demonstrated that FVT can enhance the proliferation of the commensal *Akkermansia muciniphila* and unexpectedly increase fertility rates in recipient mice, without triggering broad intestinal immune activation. These findings suggest that phage-mediated microbiome modulation may influence host physiology through subtle ecological shifts. Furthermore, another study[50] proposed a chemostat-propagated FVT approach to mitigate donor variability and infection risks associated with conventional FVT, showing promising efficacy in a *C. difficile* infection model. Together, these studies highlight the therapeutic versatility of FVT. In parallel, Ritz and colleagues[51] extended the therapeutic scope of FVT to the microbiota-gut-brain axis. They demonstrated that transferring the fecal virome from healthy, non-stressed mice to mice undergoing chronic social stress can prevent stress-associated behavioral issues and restore stress-induced changes in immune cell populations, cytokine release, bacteriome alterations, and gene expression in the amygdala. These results support the idea that phages may function as independent therapeutic agents and may contribute to the efficacy traditionally attributed to broader FMT preparations.

In human trials, fecal filtrate transfer (FFT) has also been investigated (Figure 1). In a double-blinded study of patients with metabolic syndrome, FFT induced transient changes in the phageome within 48 h.[52] While these changes were not sustained long-term, they were accompanied by measurable improvements in glucose variability at 28 days, suggesting that even short-term virome modulation might have functional consequences. Interestingly, the degree of phageome similarity between donor and recipient appeared to influence the magnitude of the response, echoing findings from bacterial FMT and reinforcing the notion that donor-recipient matching at the viral level could be relevant to the success of the procedure. In a pilot trial using FFT in rCDI patients, Ott and colleagues[53] showed that five out of five patients benefited. The filtrate contained complex phage signatures, supporting potential phage contributions. These findings hint that the virome could potentially function as an independent therapeutic component of FMT.

While the mechanisms are not fully understood, accumulating reports suggest that phages in FMT, FFT, and FVT could trigger a change in the recipient's ecosystem to resemble the donor's, potentially transferring phenotypic traits. Whether this occurs via direct predation, immunomodulation, or the HGT of microbial functions remains an open question. However, we suggest that the ability of phages to mobilize genetic material not only adds a further layer of complexity to their role in gut microbiota transplantation but may, in fact, represent a key mechanism driving microbial adaptation and functional integration in the host.

VEHICLES OF EXCHANGE: PHAGES AS MEDIATORS OF HGT

The significance of HGT as a fundamental driver of rapid microbial evolution and adaptation in microbial communities has gained widespread recognition in recent years.[54,55] Three primary mechanisms facilitate the exchange of genetic material between microbial cells. Transformation involves the uptake of extracellular DNA by naturally competent bacterial cells. Conjugation is characterized by direct cell-to-cell contact and is typically mediated by plasmids or integrative and conjugative elements. In transduction phages, VLPs or membrane vesicles

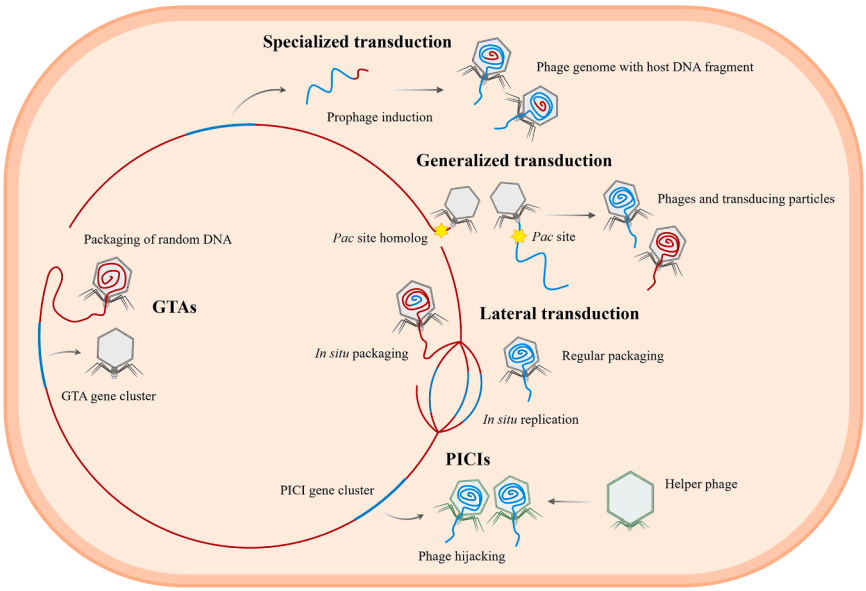


Figure 2. Phage-mediated horizontal gene transfer mechanisms

Major mechanisms of phage-mediated horizontal gene transfer (HGT). Blue represents phage DNA, and red represents bacterial chromosomal DNA. Specialized transduction consist of imprecise prophage excision that carries adjacent host sequences. In generalized transduction, packaging errors caused by pac-like motifs lead to incorporation of bacterial DNA into phage heads. In lateral transduction, in situ replication and packaging from the prophage pac site generate particles containing large contiguous regions of the chromosome. Phage-inducible chromosomal islands hijack the assembly machinery of helper phages to package their own genomes. Gene transfer agents package short, random fragments of bacterial DNA into small phage-like particles.

serve as vectors for the transfer of genetic material.[56] Phages can obviously contribute to transformation-mediated HGT by lysing bacterial cells and releasing their genomic contents into the environment, while temperate phages can act directly as vectors for horizontal gene transfer of bacterial genes, including antibiotic resistance determinants and metabolic functions, through several distinct mechanisms.[10]

The primary mechanisms of phage-mediated HGT include specialized transduction, generalized transduction, lateral transduction, and mobilization by parasitic phage satellites in the form of phage-inducible chromosomal islands (PICIs) or phage-like gene transfer agents (GTAs) (Figure 2). Specialized transduction occurs when temperate phages excise imprecisely from their host chromosome and package adjacent bacterial genes together with viral DNA. A classic example involves the lambda phage in *E. coli*, which can transfer the galactose operon or biotin synthesis genes located near its integration site. More recently, lateral transduction has emerged as a mechanism in which prophages initiate *in situ* replication and package contiguous chromosomal regions extending far beyond the prophage locus. This recently discovered system enables the transfer of much more distant DNA segments than specialized transduction, with staphylococcal phages capable of mobilizing genes across hundreds of kilobases of chromosomal DNA, including entire pathogenicity islands.[25,57] Generalized transduction involves the random packaging of phage-genome-sized bacterial DNA fragments during phage assembly, allowing transfer of all bacterial genes. P1 phage in *E. coli* is a well-studied example. GTAs are VLPs that randomly package and transfer bacterial DNA, facilitating broad horizontal transfer across bacterial populations.[26] *Caulobacter crescentus* is one example of a bacterium that has been demonstrated to produce *bona fide* GTA particles.[58] PICIs represent another transfer mechanism, where mobile genetic elements hijack phage assembly machinery, suppressing phage replication while packaging their own DNA. Superantigen-carrying staphylococcal pathogenicity islands (SaPIs) employ a related piggybacking strategy during lateral transduction.[23,24]

The role of phages in bacterial evolution and gene exchange is well-established,[59,60] while recent metagenomic analyses have expanded our understanding of the complexity of the gut phageome and its dynamic interactions with its bacterial hosts.[61,62] The significance of this field is underscored by the global rise in antimicrobial resistance, with horizontal gene transfer *via* phages contributing to the spread of resistance genes and virulence factors, highlighting the clinical relevance of phage-mediated gene transfer.[63,64] Phage-mediated HGT also extends to the exchange of genes encoding various metabolic functions. For instance, a recent study[65] showed that viral contigs isolated from mice can carry functions associated with amino acid degradation, sulfur cycling, and cofactor or vitamin biosynthesis, frequently linked to genetic exchanges with dominant gut bacterial families such as *Ruminococcaceae*, *Lachnospiraceae*, and *Bacteroidaceae*. These observations suggest that phages not only act as vehicles for adaptive traits under selective pressures, such as antibiotics, but also serve as reservoirs and distributors of metabolic traits.

Building on this, recent studies have begun to explore HGT in the context of FMT, positioning temperate phages as potential vectors of horizontal gene exchange between donor and recipient microbiomes. A study[66] on FMT from a single healthy donor to ulcerative colitis patients tracked phage-mediated transfer using metagenomic sequencing of purified viral particles. Donor-derived phages, particularly members of the now reclassified Siphoviridae family, were frequently detected in recipients, with up to 32 viral contigs transferred per individual. The majority of transferred genes were linked to temperate phage replication, including markers of lysogeny such as RepA and integrase domains. These findings suggest that lysogeny may increase phage survival and transmission across hosts, likely by allowing prophages to persist through environmental stresses encountered during fecal transfer. Subsequently, a more recent study[67] observed the highest engraftment rate in patients with rCDI post-FMT, with most of the engrafted phages being temperate. Interestingly, a higher proportion of auxiliary metabolic genes (AMGs) was identified on temperate phages. These AMGs have the potential to support and modulate bacterial metabolism. A recent placebo-controlled FMT trial in adolescents with obesity[68]

examined HGT in the gut using metagenomic data. While overall HGT rates did not differ between FMT and placebo groups, donor-derived strains that successfully engrafted promoted gene transfer to resident microbes. These transferred genes persisted for up to 26 weeks, indicating that HGT may serve as a mechanism by which donor microbiota influence recipient communities, even in the absence of long-term donor strain persistence. Together, these findings highlight the potential role of temperate phages as vehicles for gene exchange across individuals. Phage-mediated HGT may therefore represent an underappreciated mechanism by which donor-derived microbiota exerts long-term functional effects on recipient gut communities, independently of bacterial strain persistence.

The emerging evidence from FMT studies raises critical questions about the mechanisms underlying successful microbial engraftment and treatment efficacy. While donor strain colonization and recipient strain resilience appear to be key for clinical outcomes in most cases, the recently identified correlation between phage presence and therapeutic success[46] suggests a more complex relationship between viral and bacterial components of the transplanted microbiome. This observation prompts fundamental questions about whether phage-mediated HGT contributes to microbial engraftment success in FMT by facilitating the adaptation of donor strains to the recipient gut environment, improving the stability of the transplanted ecosystem, and potentially transferring beneficial genes that expand the functional capacity of the recipient microbiome beyond what is achieved through strain engraftment alone. Nevertheless, it is also important to consider that phage-mediated HGT can transfer genes with potentially harmful effects (from a human perspective), including antibiotic resistance determinants, virulence-associated factors, or other traits that may negatively impact host health.

BEYOND ENGRAFTMENT: WHY HGT DESERVES ATTENTION IN FMT

We propose that the ability of donor strains to engraft in recipients following FMT may be enhanced by gene acquisition through HGT. For instance, the survival and engraftment of donor strains may depend on rapid genetic adaptation rather than solely on their original genomic repertoire. Phage-mediated HGT provides donor strains with access to a novel genetic reservoir of the recipient microbiome, facilitating rapid adaptation to recipient-specific environmental conditions.[69] Moreover, temperate phages that integrate into donor bacterial chromosomes not only survive the transfer process but also maintain the potential for future gene mobilization. Prophage carriage can also provide immediate ecological advantages. These include immunity against superinfection by related phages and the ability to release viral particles that can infect and suppress prophage-free competitors. This creates a strong selective pressure for bacteria to acquire and retain prophages as they enter new environments, as demonstrated recently.[27,69] This pressure creates a dynamic system where donor strains could rapidly adapt to the recipient gut environment through ongoing phage-mediated gene exchange, which would explain why, after successful FMT outcomes, some donor strains are capable of stable and long-term colonization while others fail to engraft.[68] By acquiring locally advantageous genes, incoming bacteria may engraft more successfully into the resident microbiome, filling ecological niches that would otherwise remain inaccessible. Advantageous traits could include metabolic functions tuned to the recipient's diet, tolerance to bile acids or antimicrobials, colonization and competition factors, or immunomodulatory properties that help the strain coexist within the host. In this way, HGT can be envisioned as a shortcut to ecological compatibility, allowing donor strains to gain fitness benefits. Such events could determine whether incoming bacteria are transient or become established members of the gut community. Moreover, modeling and comparative genomics suggest that maintaining high strain diversity in microbial communities is essentially impossible without HGT, including phage-driven HGT. By altering growth rates through mobile genes and promoting the transfer of antibiotic-resistant or other adaptive elements, HGT enhances species coexistence and resilience, allowing more strains to survive and occupy overlapping niches.[70] These findings support the idea that gene flow via HGT not only benefits individual donor strains but also contributes to the overall stability and functional diversity of the gut microbiome.

Importantly, adaptive gene acquisition may not only benefit donor strains. Phage-mediated HGT could also allow the recipient microbiota to acquire donor-derived functional traits without the need for colonization. This could explain those cases in which FMT improves clinical outcomes even when donor strains fail to establish long-term residency.[71,72] For example, phage-mediated transfer of genes encoding carbohydrate-active enzymes, stress tolerance factors, or biosynthetic pathways could rapidly expand the functional potential of the existing microbiota. The resulting hybrid community may have new metabolic capabilities or resilience, thereby restoring gut homeostasis even in the absence of extensive donor strain engraftment.

Therefore, the current focus on bacterial engraftment in FMT research may overlook fundamental mechanisms underlying the efficacy of the procedure. Traditional metagenomic approaches that emphasize taxonomic composition and abundance may miss functionally significant gene transfer events, particularly when donor strains do not persist long-term. This methodological blind spot could lead to the underestimation of donor microbiome impact, and cases where FMT appears successful despite poor donor strain engraftment might actually represent successful HGT events that remain undetected by conventional analysis approaches.

The gut microbiome represents a dynamic genetic ecosystem. By embracing this complexity and bringing HGT into the conversation, FMT research can advance beyond simplistic engraftment models toward a deeper understanding of microbial communities and microbial therapy.

TRANSLATIONAL AND RESEARCH ROADMAP: TESTING THE ROLE OF PHAGES IN FMT

The conceptual model we propose (Figure 3) frames FMT as a dynamic encounter between the genetic complement of both donor and recipient microbial ecosystems, in which phages can act as vectors of bidirectional gene exchange and drivers of rapid microbial adaptation. Donor phages could transfer advantageous genes to recipient bacteria. Likewise, recipient

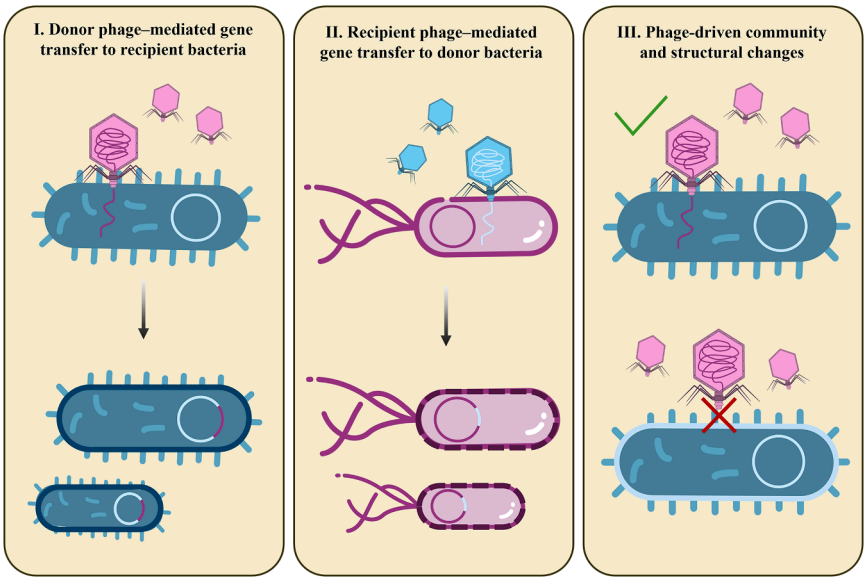


Figure 3. Propose model of potential phage-mediated interactions and gene-transfer events following fecal microbiota transplantation

Donor-derived phages and bacteria (pink) enter a recipient community (blue), enabling several possible outcomes. (I) Donor phages may transfer genetic material to recipient bacteria, with consequences that depend on the functions transferred. (II) Recipient transducing particles may infect donor strains and deliver recipient DNA, potentially aiding donor adaptation and engraftment. (III) Donor-phage activity may also drive rapid evolutionary responses in recipient populations, such as surface or receptor alterations, even in the absence of horizontal gene transfer. We propose that all of them: HGT from donor phage to recipient bacteria, from recipient phage to donor bacteria, as well as lytic activity of the phage, result in phenotypic changes at the population level (within species), and at the community level (species/strain composition).

phages could confer adaptive traits to donor strains, potentially improving their engraftment. Beyond HGT, phages may also promote rapid microevolution through mechanisms such as stimulation of bacterial phase variation or surface modifications that may alter susceptibility and niche access. However, if phage-mediated HGT contributes meaningfully to engraftment, functional restoration, or long-term microbiome stability, then its role must be evaluated experimentally.

With currently available tools, substantial progress can be made by integrating virome analyses into existing and future FMT studies. Paired donor-recipient sampling before and after transplantation, combined with paired bacteriome (total community DNA) and virome (VLP DNA) sequencing datasets, can enable tracking of phage persistence alongside bacterial strain dynamics.[21] Importantly, these datasets should move beyond taxonomic composition to include functional annotation of bacterial and viral genomes, enabling detection of AMGs, lysogeny-associated modules, PICI, prophage-proximal regions (lateral transduction), or random packaging of bacterial DNA (generalized transduction, GTA). Targeted tracking of putative phage-mobilized genes over time would provide indirect but informative evidence for phage-mediated HGT *in vivo*. Reanalysis of existing FMT metagenomic datasets with this integrative lens could already test whether successful clinical outcomes correlate with increased gene flow, phage persistence, or functional convergence between donor and recipient microbiomes. Within this framework, donor-derived phages carrying lysogeny-associated modules or AMGs, PICI, prophage-proximal regions, or entire genomes containing GTA could be monitored as potential vectors of gene transfer to resident recipient bacteria, addressing the first mechanism proposed in Figure 3.

At the same time, baseline characterization of the recipient virome and bacteriome may provide insights into the ecological permissiveness for incoming strains. Monitoring changes in prophage content within engrafting donor bacteria would allow for the assessment of gene acquisition from recipient-associated phages, directly probing the second mechanism proposed in Figure 3. Across both contexts, functional annotation of viral genomes, including screening for antibiotic resistance or virulence-associated genes, would help distinguish adaptive gene transfer events from those with potentially adverse consequences for host health and align mechanistic insights with translational considerations.

Addressing causality will require experimental designs capable of disentangling phage-driven effects from broader microbial community changes. One approach would be the systematic comparison of component-separated interventions (FMT, FFT, and FVT) using standardized preparations. Comparing ecological and functional outcomes across these interventions can help identify which effects track specifically with the virome fraction.

Controlled experimental systems offer further solutions. Defined synthetic communities of virulent phage-free bacteria, communities of phages, or combinations thereof, as well as *in vitro* chemostats, artificial gut models, and gnotobiotic animal models, can be used to disentangle the directionality of gene flow. These models could explicitly test donor-to-recipient HGT, as well as phage-driven processes such as bacterial phase variation or surface modification. These systems are particularly well-suited for testing the third mechanism in Figure 3, namely phage-driven community and structural changes, under conditions where confounding variables can be better controlled.

Over longer time horizons, mechanistic insights into phage-mediated processes could inform a more refined approach to FMT. Rather than attempting to exert direct control over phage communities, a more realistic goal is to systematically characterize virome features in donors and recipients and evaluate how these features relate to engraftment, functional integration, and clinical outcomes. Measures such as phage diversity, abundance proxies, and the balance between temperate and lytic lifestyles could be considered alongside bacterial profiling during donor selection.

Recipient baseline states, including compatibility with donor viromes, may further explain interindividual variability in

response to FMT. Importantly, translational implementation must account for potential risks associated with phage-mediated gene transfer, particularly the mobilization of antibiotic resistance or virulence determinants. Integrating safety-oriented screening with mechanistic understanding should be essential for responsible clinical application.

By aligning conceptual models with concrete experimental and clinical strategies, future studies can move beyond correlation and toward a mechanistic understanding of how phages contribute to the outcomes of microbiota-based therapies.

CONCLUSION

In this perspective, we discuss one of the least investigated roles of phages in FMT. This is their capacity to mediate HGT and thus act as active participants rather than passive elements during the engraftment process. Although the current evidence remains limited and often indirect, we suggest that phages transferred during FMT may not simply accompany bacterial communities but could influence gut ecosystems in subtler, yet potentially consequential, ways.

While FMT research has traditionally centered on bacterial engraftment and community restructuring, evidence increasingly shows that donor-derived phages engraft and persist after FMT.[20,21] Importantly, phage richness and the presence of specific viral taxa correlate with successful treatment outcomes.[44–46] While these correlations do not establish causality, they suggest that phages could contribute to FMT success in some way, whether through modulation of bacterial population dynamics, functional shifts, or alterations in the overall community diversity and resilience. Experimental work further shows that virome transfer alone can induce ecological, metabolic, physiologic, and behavioral changes in animal models,[39,47,48,51] implying that phages might exert measurable effects independently of bacterial cells.

Temperate phages frequently carry and mobilize bacterial genes, including those responsible for virulence, phage defense, antimicrobial activity, and resistance to it, and metabolic capacities.[10,65] FMT studies have documented the transfer of donor phages containing lysogeny modules and AMGs into recipients,[66,67] and donor-derived strains that engraft may promote gene exchange with the resident microbiota.[68] While such gene flow could support ecological integration and functional restoration, it may also carry risks, including the potential movement of antibiotic resistance or virulence genes.[63]

Based on these conclusions, we advocate for the integration of virome profiling into clinical FMT protocols. Donor selection should incorporate phage diversity metrics alongside bacterial screening criteria, and experimental designs should consider the detection of donor-to-recipient and recipient-to-donor HGT events. The field requires the development of genomic approaches capable of tracking gene transfer across microbial communities, moving beyond taxonomic composition analysis to capture the genetic exchanges.

DECLARATION OF INTERESTS

The authors declare no competing interests.

REFERENCES

1. Pasolli, E., Asnicar, F., Manara, S., Zolfo, M., Karcher, N., Armanini, F., Beghini, F., Manghi, P., Tett, A., Ghensi, P., et al. (2019). Extensive unexplored human microbiome diversity revealed by over 150,000 genomes from metagenomes spanning age, geography, and lifestyle. Cell *176*, 649–662.e20. https://doi.org/10.1016/j.cell.2019.01.001.

2. Shen, J., Zhang, J., Mo, L., Li, Y., Li, Y., Li, C., Kuang, X., Tao, Z., Qu, Z., Wu, L., et al. (2023). Large-scale phage cultivation for commensal human gut bacteria. Cell Host Microbe *31*, 665–677.e7. https://doi.org/10.1016/j.chom.2023.03.013.

3. Mahmud, M.R., Tamanna, S.K., Akter, S., Mazumder, L., Akter, S., Hasan, M.R., Acharjee, M., Esti, I.Z., Islam, M.S., Shihab, M.M.R., et al. (2024). Role of bacteriophages in shaping gut microbial community. Gut Microbes *16*, 2390720. https://doi.org/10.1080/19490976.2024.2390720.

4. Shkoporov, A.N., Khokhlova, E.V., Stephens, N., Hueston, C., Seymour, S., Hryckowian, A.J., Scholz, D., Ross, R.P., and Hill, C. (2021). Long-term persistence of crAss-like phage crAss001 is associated with phase variation in Bacteroides intestinalis. BMC Biol. *19*, 163. https://doi.org/10.1186/s12915-021-01084-3.

5. Castledine, M., and Buckling, A. (2024). Critically evaluating the relative importance of phage in shaping microbial community composition. Trends Microbiol. *32*, 957–969. https://doi.org/10.1016/j.tim.2024.02.014.

6. Culp, E.J., and Goodman, A.L. (2023). Cross-feeding in the gut microbiome: ecology and mechanisms. Cell Host Microbe *31*, 485–499. https://doi.org/10.1016/j.chom.2023.03.016.

7. Coyte, K.Z., and Rakoff-Nahoum, S. (2019). Understanding competition and cooperation within the mammalian gut microbiome. Curr. Biol. *29*, R538–R544. https://doi.org/10.1016/j.cub.2019.04.017.

8. Alseth, E.O., Custodio, R., Sundius, S.A., Kuske, R.A., Brown, S.P., and Westra, E.R. (2024). The impact of phage and phage resistance on microbial community dynamics. PLoS Biol. *22*, e3002346. https://doi.org/10.1371/journal.pbio.3002346.

9. Shkoporov, A.N., Clooney, A.G., Sutton, T.D.S., Ryan, F.J., Daly, K.M., Nolan, J.A., McDonnell, S.A., Khokhlova, E.V., Draper, L.A., Forde, A., et al. (2019). The human gut virome is highly diverse, stable, and individual specific. Cell Host Microbe *26*, 527–541.e5. https://doi.org/10.1016/j.chom.2019.09.009.

10. Borodovich, T., Shkoporov, A.N., Ross, R.P., and Hill, C. (2022). Phage-mediated horizontal gene transfer and its implications for the human gut microbiome. Gastroenterol. Rep. (Oxf) *10*, goac012. https://doi.org/10.1093/gastro/goac012.

11. Lloyd-Price, J., Abu-Ali, G., and Huttenhower, C. (2016). The healthy human microbiome. Genome Med. *8*, 51. https://doi.org/10.1186/s13073-016-0307-y.

12. Arpaia, N., Campbell, C., Fan, X., Dikiy, S., Van Der Veeken, J., Deroos, P., Liu, H., Cross, J.R., Pfeffer, K., Coffer, P.J., et al. (2013). Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation. Nature *504*, 451–455. https://doi.org/10.1038/nature12726.

13. Swann, J.R., Want, E.J., Geier, F.M., Spagou, K., Wilson, I.D., Sidaway, J.E., Nicholson, J.K., and Holmes, E. (2011). Systemic gut microbial modulation of bile acid metabolism in host tissue compartments. Proc. Natl. Acad. Sci. USA *108*, 4523–4530. https://doi.org/10.1073/pnas.1006734107.

14. Spigaglia, P. (2024). Clostridioides difficile and gut microbiota: from colonization to infection and treatment. Pathogens *13*, 646. https://doi.org/10.3390/pathogens13080646.

15. Fenneman, A.C., Weidner, M., Chen, L.A., Nieuwdorp, M., and Blaser, M.J. (2023). Antibiotics in the pathogenesis of diabetes and inflammatory diseases of the gastrointestinal tract. Nat. Rev. Gastroenterol. Hepatol. *20*, 81–100. https://doi.org/10.1038/s41575-022-00685-9.

16. Fan, Y., and Pedersen, O. (2021). Gut microbiota in human metabolic health and disease. Nat. Rev. Microbiol. *19*, 55–71. https://doi.org/10.1038/s41579-020-0433-9.

17. Mocanu, V., Zhang, Z., Deehan, E.C., Kao, D.H., Hotte, N., Karmali, S., Birch, D.W., Samarasinghe, K.K., Walter, J., and Madsen, K.L. (2021).

Fecal microbial transplantation and fiber supplementation in patients with severe obesity and metabolic syndrome: a randomized double-blind, placebo-controlled phase 2 trial. Nat. Med. *27*, 1272–1279. https://doi.org/10.1038/s41591-021-01399-2.

18. Khoruts, A., Staley, C., and Sadowsky, M.J. (2021). Faecal microbiota transplantation for Clostridioides difficile: mechanisms and pharmacology. Nat. Rev. Gastroenterol. Hepatol. *18*, 67–80. https://doi.org/10.1038/s41575-020-0350-4.

19. Hvas, C.L., Dahl Jørgensen, S.M.D., Jørgensen, S.P., Storgaard, M., Lemming, L., Hansen, M.M., Erikstrup, C., and Dahlerup, J.F. (2019). Fecal microbiota transplantation is superior to fidaxomicin for treatment of recurrent Clostridium difficile infection. Gastroenterology *156*, 1324–1332.e3. https://doi.org/10.1053/j.gastro.2018.12.019.

20. Zuppi, M., Vatanen, T., Wilson, B.C., Golovina, E., Portlock, T., Cutfield, W.S., Vickers, M.H., and O'Sullivan, J.M. (2024). Fecal microbiota transplantation alters gut phage communities in a clinical trial for obesity. Microbiome *12*, 122. https://doi.org/10.1186/s40168-024-01833-w.

21. Draper, L.A., Ryan, F.J., Smith, M.K., Jalanka, J., Mattila, E., Arkkila, P.A., Ross, R.P., Satokari, R., and Hill, C. (2018). Long-term colonisation with donor bacteriophages following successful faecal microbial transplantation. Microbiome *6*, 220. https://doi.org/10.1186/s40168-018-0598-x.

22. Groussin, M., Poyet, M., Sistiaga, A., Kearney, S.M., Moniz, K., Noel, M., Hooker, J., Gibbons, S.M., Segurel, L., Froment, A., et al. (2021). Elevated rates of horizontal gene transfer in the industrialized human microbiome. Cell *184*, 2053–2067.e18. https://doi.org/10.1016/j.cell.2021.02.052.

23. Chee, M.S.J., Serrano, E., Chiang, Y.N., Harling-Lee, J., Man, R., Bacigalupe, R., Fitzgerald, J.R., Penadés, J.R., and Chen, J. (2023). Dual pathogenicity island transfer by piggybacking lateral transduction. Cell *186*, 3414–3426.e16. https://doi.org/10.1016/j.cell.2023.07.001.

24. Fillol-Salom, A., Rostøl, J.T., Ojiogu, A.D., Chen, J., Douce, G., Humphrey, S., and Penadés, J.R. (2022). Bacteriophages benefit from mobilizing pathogenicity islands encoding immune systems against competitors. Cell *185*, 3248–3262.e20. https://doi.org/10.1016/j.cell.2022.07.014.

25. Humphrey, S., Fillol-Salom, A., Quiles-Puchalt, N., Ibarra-Chávez, R., Haag, A.F., Chen, J., and Penadés, J.R. (2021). Bacterial chromosomal mobility via lateral transduction exceeds that of classical mobile genetic elements. Nat. Commun. *12*, 6509. https://doi.org/10.1038/s41467-021-26004-5.

26. Kleiner, M., Bushnell, B., Sanderson, K.E., Hooper, L.V., and Duerkop, B.A. (2020). Transductomics: sequencing-based detection and analysis of transduced DNA in pure cultures and microbial communities. Microbiome *8*, 158. https://doi.org/10.1186/s40168-020-00935-5.

27. Frazão, N., Konrad, A., Amicone, M., Seixas, E., Güleresi, D., Lässig, M., and Gordo, I. (2022). Two modes of evolution shape bacterial strain diversity in the mammalian gut for thousands of generations. Nat. Commun. *13*, 5604. https://doi.org/10.1038/s41467-022-33412-8.

28. Borodovich, T., Buttimer, C., Wilson, J.S., Bardy, P., Smith, M., Hill, C., Khokhlova, E.V., Harte, M., Govi, B., Fogg, P.C.M., et al. (2026). Large-scale capsid-mediated mobilisation of bacterial genomic DNA in the gut microbiome. Nat. Commun. *17*, 2046. https://doi.org/10.1038/s41467-026-68726-4.

29. Zuppi, M., Hendrickson, H.L., O'Sullivan, J.M., and Vatanen, T. (2022). Phages in the gut ecosystem. Front. Cell. Infect. Microbiol. *11*, 822562. https://doi.org/10.3389/fcimb.2021.822562.

30. Pargin, E., Roach, M.J., Skye, A., Papudeshi, B., Inglis, L.K., Mallawaarachchi, V., Grigson, S.R., Harker, C., Edwards, R.A., and Giles, S.K. (2023). The human gut virome: composition, colonization, interactions, and impacts on human health. Front. Microbiol. *14*, 963173. https://doi.org/10.3389/fmicb.2023.963173.

31. Lopez, J.A., McKeithen-Mead, S., Shi, H., Nguyen, T.H., Huang, K.C., and Good, B.H. (2025). Abundance measurements reveal the balance between lysis and lysogeny in the human gut microbiome. Curr. Biol. *35*, 2282–2294.e11. https://doi.org/10.1016/j.cub.2025.03.073.

32. Ofir, G., and Sorek, R. (2018). Contemporary phage biology: from classic models to new insights. Cell *172*, 1260–1270. https://doi.org/10.1016/j.cell.2017.10.045.

33. Henrot, C., and Petit, M.A. (2022). Signals triggering prophage induction in the gut microbiota. Mol. Microbiol. *118*, 494–502. https://doi.org/10.1111/mmi.14983.

34. Huang, Y., Wang, T., and Ma, Y. (2025). Gut microbiome: Temperate and latent phages are dominant in the human gut. Curr. Biol. *35*, R377–R379. https://doi.org/10.1016/j.cub.2025.01.006.

35. Reyes, A., Wu, M., McNulty, N.P., Rohwer, F.L., and Gordon, J.I. (2013). Gnotobiotic mouse model of phage–bacterial host dynamics in the human gut. Proc. Natl. Acad. Sci. USA *110*, 20236–20241. https://doi.org/10.1073/pnas.1319470110.

36. Wilde, J., Boyes, R., Robinson, A.V., Daisley, B.A., Botschner, A.J., Brettingham, D.J.L., Macpherson, C.V., Mallory, E., and Allen-Vercoe, E. (2024). Assessing phage-host population dynamics by reintroducing virulent viruses to synthetic microbiomes. Cell Host Microbe *32*, 768–778.e9. https://doi.org/10.1016/j.chom.2024.04.001.

37. Castledine, M., Padfield, D., Lewis, R., and Buckling, A. (2025). Microbial community structure is affected by phage-resistance associated increases in host density. FEMS Microbiol. Ecol. *101*, fiaf027. https://doi.org/10.1093/femsec/fiaf027.

38. Campbell, D.E., Ly, L.K., Ridlon, J.M., Hsiao, A., Whitaker, R.J., and Degnan, P.H. (2020). Infection with bacteroides phage BV01 alters the host transcriptome and bile acid metabolism in a common human gut microbe. Cell Rep. *32*, 108142. https://doi.org/10.1016/j.celrep.2020.108142.

39. Hsu, B.B., Gibson, T.E., Yeliseyev, V., Liu, Q., Lyon, L., Bry, L., Silver, P.A., and Gerber, G.K. (2019). Dynamic modulation of the gut microbiota and metabolome by bacteriophages in a mouse model. Cell Host Microbe *25*, 803–814.e5. https://doi.org/10.1016/j.chom.2019.05.001.

40. Buttimer, C., Sutton, T., Colom, J., Murray, E., Bettio, P.H., Smith, L., Bolocan, A.S., Shkoporov, A., Oka, A., Liu, B., et al. (2022). Impact of a phage cocktail targeting Escherichia coli and Enterococcus faecalis as members of a gut bacterial consortium in vitro and in vivo. Front. Microbiol. *13*, 936083. https://doi.org/10.3389/fmicb.2022.936083.

41. Jdeed, G., Kravchuk, B., and Tikunova, N.V. (2025). Factors affecting phage–bacteria coevolution dynamics. Viruses *17*, 235. https://doi.org/10.3390/v17020235.

42. Broecker, F., Russo, G., Klumpp, J., and Moelling, K. (2017). Stable core virome despite variable microbiome after fecal transfer. Gut Microbes *8*, 214–220. https://doi.org/10.1080/19490976.2016.1265196.

43. Zhou, H., Tang, L., Fenton, K.A., and Song, X. (2025). Exploring and evaluating microbiome resilience in the gut. FEMS Microbiol. Ecol. *101*, fiaf046. https://doi.org/10.1093/femsec/fiaf046.

44. Park, H., Laffin, M.R., Jovel, J., Millan, B., Hyun, J.E., Hotte, N., Kao, D., and Madsen, K.L. (2019). The success of fecal microbial transplantation in Clostridium difficile infection correlates with bacteriophage relative abundance in the donor: a retrospective cohort study. Gut Microbes *10*, 676–687. https://doi.org/10.1080/19490976.2019.1586037.

45. Manrique, P., Zhu, Y., van der Oost, J., Herrema, H., Nieuwdorp, M., de Vos, W.M., and Young, M. (2021). Gut bacteriophage dynamics during fecal microbial transplantation in subjects with metabolic syndrome. Gut Microbes *13*, 1–15. https://doi.org/10.1080/19490976.2021.1897217.

46. Zuo, T., Wong, S.H., Lam, K., Lui, R., Cheung, K., Tang, W., Ching, J.Y.L., Chan, P.K.S., Chan, M.C.W., Wu, J.C.Y., et al. (2018). Bacteriophage transfer during faecal microbiota transplantation in Clostridium difficile infection is associated with treatment outcome. Gut *67*, 634–643. https://doi.org/10.1136/gutjnl-2017-313952.

47. Mao, X., Larsen, S.B., Zachariassen, L.S.F., Brunse, A., Adamberg, S., Mejia, J.L.C., Larsen, F., Adamberg, K., Nielsen, D.S., Hansen, A.K., et al. (2024). Transfer of modified gut viromes improves symptoms associated with metabolic syndrome in obese male mice. Nat. Commun. *15*, 4704. https://doi.org/10.1038/s41467-024-49152-w.

48. Rasmussen, T.S., Mentzel, C.M.J., Kot, W., Castro-Mejía, J.L., Zuffa, S., Swann, J.R., Hansen, L.H., Vogensen, F.K., Hansen, A.K., and Nielsen, D.S. (2020). Faecal virome transplantation decreases symptoms of type 2 diabetes and obesity in a murine model. Gut *69*, 2122–2130. https://doi.org/10.1136/gutjnl-2019-320005.

49. Rasmussen, T.S., Mentzel, C.M.J., Danielsen, M.R., Jakobsen, R.R., Zachariassen, L.S.F., Castro Mejia, J.L., Brunse, A., Hansen, L.H., Hansen, C.H.F., Hansen, A.K., et al. (2023). Fecal virome transfer improves proliferation of commensal gut Akkermansia muciniphila and unexpectedly enhances the fertility rate in laboratory mice. Gut Microbes *15*, 2208504. https://doi.org/10.1080/19490976.2023.2208504.

50. Rasmussen, T.S., Mao, X., Forster, S., Larsen, S.B., Von Münchow, A., Tranæs, K.D., Brunse, A., Larsen, F., Mejia, J.L.C., Adamberg, S., et al. (2024). Overcoming donor variability and risks associated with fecal microbiota transplants through bacteriophage-mediated treatments. Microbiome *12*, 119. https://doi.org/10.1186/s40168-024-01820-1.

51. Ritz, N.L., Draper, L.A., Bastiaanssen, T.F.S., Turkington, C.J.R., Peterson, V.L., van de Wouw, M., Vlckova, K., Fülling, C., Guzzetta, K.E., Burokas, A., et al. (2024). The gut virome is associated with stress-induced changes in behaviour and immune responses in mice. Nat. Microbiol. *9*, 359–376. https://doi.org/10.1038/s41564-023-01564-y.

52. Wortelboer, K., de Jonge, P.A., Scheithauer, T.P.M., Attaye, I., Kemper, E.M., Nieuwdorp, M., and Herrema, H. (2023). Phage-microbe dynamics after sterile faecal filtrate transplantation in individuals with metabolic syndrome: a double-blind, randomised, placebo-controlled clinical trial assessing efficacy and safety. Nat. Commun. *14*, 5600. https://doi.org/10.1038/s41467-023-41329-z.

53. Ott, S.J., Waetzig, G.H., Rehman, A., Moltzau-Anderson, J., Bharti, R., Grasis, J.A., Cassidy, L., Tholey, A., Fickenscher, H., Seegert, D., et al. (2017). Efficacy of sterile fecal filtrate transfer for treating patients with Clostridium difficile infection. Gastroenterology *152*, 799–811.e7. https://doi.org/10.1053/j.gastro.2016.11.010.

54. Tokuda, M., and Shintani, M. (2024). Microbial evolution through horizontal gene transfer by mobile genetic elements. Microb. Biotechnol. *17*, e14408. https://doi.org/10.1111/1751-7915.14408.

55. Yaffe, E., and Relman, D.A. (2020). Tracking microbial evolution in the human gut using Hi-C reveals extensive horizontal gene transfer, persistence and adaptation. Nat. Microbiol. *5*, 343–353. https://doi.org/10.1038/s41564-019-0625-0.

56. Moura de Sousa, J.M., Lourenço, M., and Gordo, I. (2023 Apr 12). Horizontal gene transfer among host-associated microbes. Cell Host Microbe *31*, 513–527. https://doi.org/10.1016/j.chom.2023.03.017.

57. Fillol-Salom, A., Bacigalupe, R., Humphrey, S., Chiang, Y.N., Chen, J., and Penadés, J.R. (2021). Lateral transduction is inherent to the life cycle of the archetypical Salmonella phage P22. Nat. Commun. *12*, 6510. https://doi.org/10.1038/s41467-021-26520-4.

58. Tran, N.T., and Le, T.B.K. (2024). Control of a gene transfer agent cluster in Caulobacter crescentus by transcriptional activation and anti-termination. Nat. Commun. *15*, 4749. https://doi.org/10.1038/s41467-024-49114-2.

59. Fineran, P.C., Petty, N.K., and Salmond, G.P.C. (2009). Transduction: Host DNA Transfer by Bacteriophages. In Encyclopedia of Microbiology (Elsevier), pp. 666–679. https://doi.org/10.1016/B978-012373944-5.00302-5.

60. Brabban, A.D., Hite, E., and Callaway, T.R. (2005). Evolution of foodborne pathogens via temperate bacteriophage-mediated gene transfer. Foodborne Pathog. Dis. *2*, 287–303. https://doi.org/10.1089/fpd.2005.2.287.

61. Lai, S., Wang, H., Bork, P., Chen, W.H., and Zhao, X.M. (2024). Long-read sequencing reveals extensive gut phageome structural variations driven by genetic exchange with bacterial hosts. Sci. Adv. *10*, eadn3316. https://doi.org/10.1126/sciadv.adn3316.

62. Camarillo-Guerrero, L.F., Almeida, A., Rangel-Pineros, G., Finn, R.D., and Lawley, T.D. (2021). Massive expansion of human gut bacteriophage diversity. Cell *184*, 1098–1109.e9. https://doi.org/10.1016/j.cell.2021.01.029.

63. Fernández-Orth, D., Miró, E., Brown-Jaque, M., Rodríguez-Rubio, L., Espinal, P., Rodriguez-Navarro, J., González-López, J.J., Muniesa, M., and Navarro, F. (2019). Faecal phageome of healthy individuals: presence of antibiotic resistance genes and variations caused by ciprofloxacin treatment. J. Antimicrob. Chemother. *74*, 854–864. https://doi.org/10.1093/jac/dky540.

64. Modi, S.R., Lee, H.H., Spina, C.S., and Collins, J.J. (2013). Antibiotic treatment expands the resistance reservoir and ecological network of the phage metagenome. Nature *499*, 219–222. https://doi.org/10.1038/nature12212.

65. Ishola, O.A., Kublik, S., Durai Raj, A.C., Ohnmacht, C., Schulz, S., Foesel, B.U., and Schloter, M. (2024). Comparative metagenomic analysis of bacteriophages and prophages in gnotobiotic mouse models. Microorganisms *12*, 255. https://doi.org/10.3390/microorganisms12020255.

66. Chehoud, C., Dryga, A., Hwang, Y., Nagy-Szakal, D., Hollister, E.B., Luna, R.A., Versalovic, J., Kellermayer, R., and Bushman, F.D. (2016). Transfer of viral communities between human individuals during fecal microbiota transplantation. mBio. *7*, e00322. https://doi.org/10.1128/mBio.00322-16.

67. Ji, S., Ahmad, F., Peng, B., Yang, Y., Su, M., Zhao, X., and Vatanen, T. (2025). Engrafting gut bacteriophages have potential to modulate microbial metabolism in fecal microbiota transplantation. Microbiome *13*, 149. https://doi.org/10.1186/s40168-025-02046-5.

68. Behling, A.H., Wilson, B.C., Ho, D., Cutfield, W.S., Vatanen, T., and O'Sullivan, J.M. (2024). Horizontal gene transfer after faecal microbiota transplantation in adolescents with obesity. Microbiome *12*, 26. https://doi.org/10.1186/s40168-024-01748-6.

69. Frazão, N., Sousa, A., Lässig, M., and Gordo, I. (2019). Horizontal gene transfer overrides mutation in Escherichia coli colonizing the mammalian gut. Proc. Natl. Acad. Sci. USA *116*, 17906–17915. https://doi.org/10.1073/pnas.1906958116.

70. Zhu, S., Hong, J., and Wang, T. (2024). Horizontal gene transfer is predicted to overcome the diversity limit of competing microbial species. Nat. Commun. *15*, 800. https://doi.org/10.1038/s41467-024-45154-w.

71. Podlesny, D., Durdevic, M., Paramsothy, S., Kaakoush, N.O., Högenauer, C., Gorkiewicz, G., Walter, J., and Fricke, W.F. (2022). Identification of clinical and ecological determinants of strain engraftment after fecal microbiota transplantation using metagenomics. Cell Rep. Med. *3*, 100711. https://doi.org/10.1016/j.xcrm.2022.100711.

72. Staley, C., Kelly, C.R., Brandt, L.J., Khoruts, A., and Sadowsky, M.J. (2016). Complete microbiota engraftment is not essential for recovery from recurrent Clostridium difficile infection following fecal microbiota transplantation. mBio. *7*. https://doi.org/10.1128/mBio.01965-16.