The Human Gut Virome at the Crossroads of Immunity, Disease and Therapeutics: A Comprehensive Review

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It is hereby declared that

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We hereby declare that the thesis entitled "The Human Gut Virome at the Crossroads of Immunity, Disease and Therapeutics: A Comprehensive Review" is from the Student's own work and effort, and all other sources of information used have been Acknowledged. This Thesis has been submitted with our approval.

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Abstract

The human gut virome, a complex and dynamic part of the gut microbiome, is an important but understudied mediator of health and disease. Encompassing bacteriophages, eukaryotic viruses, and endogenous viral elements, the gut virome is intricately linked to bacteriome, immune, and host metabolic systems, which impacts the development of diseases including inflammatory bowel disease (IBD) and metabolic diseases, and even neuropsychiatric and autoimmune diseases. The development of metagenomic sequencing techniques over the past few years has brought to light the high degree of interindividual variability of the virome, as well as its rapid response to environmental factors such as diet and antibiotics, and its age-dependent evolution. Dysbiosis in viral communities—characterized by changes in activity of temperate phages, reductions in viral diversity, or expansion of pathogenic viruses—are associated with mucosal inflammation, microbial dysbiosis, and systemic disease.

Novel treatments under development, including fecal virome transplantation (FVT) and targeted phage therapy, demonstrate the potential of the virome in re-establishing microbial balance and combatting antibiotic resistant infections. Yet, obstacles exist in organizing virome characterization, determining causal associations, and guaranteeing safety of viral-based treatment modalities. The focus of this review is to integrate current insights into the diversity and stability, as well as functional attributes of the gut virome, while stressing its reciprocal relationships with host immunity and disease development. It investigates the virome in other settings, such as inflammatory bowel disease (IBD), type 1 and type 2 diabetes, obesity, liver diseases, arthritis and neuropsychiatric conditions, and how diet, stress and geography influence viral ecology.

By combining multi-omics strategies with the personalized aspect of the virome, new biomarkers and precision therapies could be discovered in the future. This study highlights the virome as an important frontier in microbiome research with potentially transformative implications for diagnostics, therapeutics, and preventive medicine in the context of personalized health.

Acknowledgments

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Chapter 1

1. Introduction

The human gut micobiome is a large ecosystem that contains many different microorganisms, made up of bacteria, fungi, archaea, and viruses, the latter of which is collectively known as the gut virome (Tun et al., 2023). The virome, which is primarily made up of bacteriophages (phages), eukaryotic viruses, and endogenous viral elements, is emerging as an important regulator of host health, immune system function, and disease pathogenesis (Stockdale et al., 2023). With recent advances in metagenomic sequencing and bioinformatics, it has become clearer that, not only is there an untold amount of viral diversity lying within the gastrointestinal tract, but the viral community contained therein is highly individualized and also exhibits fluctuations across time scales ranging from the immediate effects of dietary intake to trends across decades of life (Focà et al., 2015). In contrast with the relatively stable nature of the bacterial microbiome, the virome is more fluid and rapidly responding to changes in environmental parameters, antibiotic treatment and disease (Sinha et al., 2022).

One of the most fascinating characteristic features with the gut virome is the reciprocal interaction it has with the bacteriome. Bacteriophages (phages), obligate intracellular parasites of bacteria, are influential in shaping the structure of the microbiota, promoting horizontal gene exchange, and preserving gut homeostasis (Pérez-Brocal et al., 2015). Slight imbalances in this delicate balance have been associated with a large variety of diseases, including inflammatory bowel disease (IBD), colorectal cancer (CRC), metabolic diseases (e.g., type 2 diabetes and obesity) and even neuropsychiatric disorders such as schizophrenia and Alzheimer’s disease (Zhao et al., 2017). For example, increased temperate phage activity has been detected in patients with IBD (where it is associated with an exacerbation of mucosal inflammation) and decreases in viral diversity have been reported in metabolic syndrome and autoimmune diseases (Fan et al., 2023).

In addition to its role in disease, the virome is beginning to be recognized as a therapeutic frontier. Fecal virome transplantation (FVT) is analogous to FMT and is effective at restoring a healthy microbial profile in mouse models of obesity and type II diabetes (Fang & Ning, 2024). Likewise, the phage therapy – goal-directed bactericidal activity through lytic phage in pathogenic bacteria – has potential against antibiotic resistant infections and as a strategy to manipulate chronic inflammatory processes (Wu et al., 2024). Nevertheless, hurdles exist on standardization of virome characterization, separating causation from association, and ethical and safety issues of viral-based therapies (Ma et al., 2018).

This review compiles recent advances in the study of the composition, stability, and functional dynamics of the human gut virome, and specifically discusses its interfacing with immunity, disease pathogenesis and therapeutic innovation. It can be proposed that incorporation of knowledge of virome-host interaction studies, can reclassify this "neglected organ" in the

microbiome and open new dimensions for precision medicine and future diagnostic/treatment modalities (Minot et al., 2011).

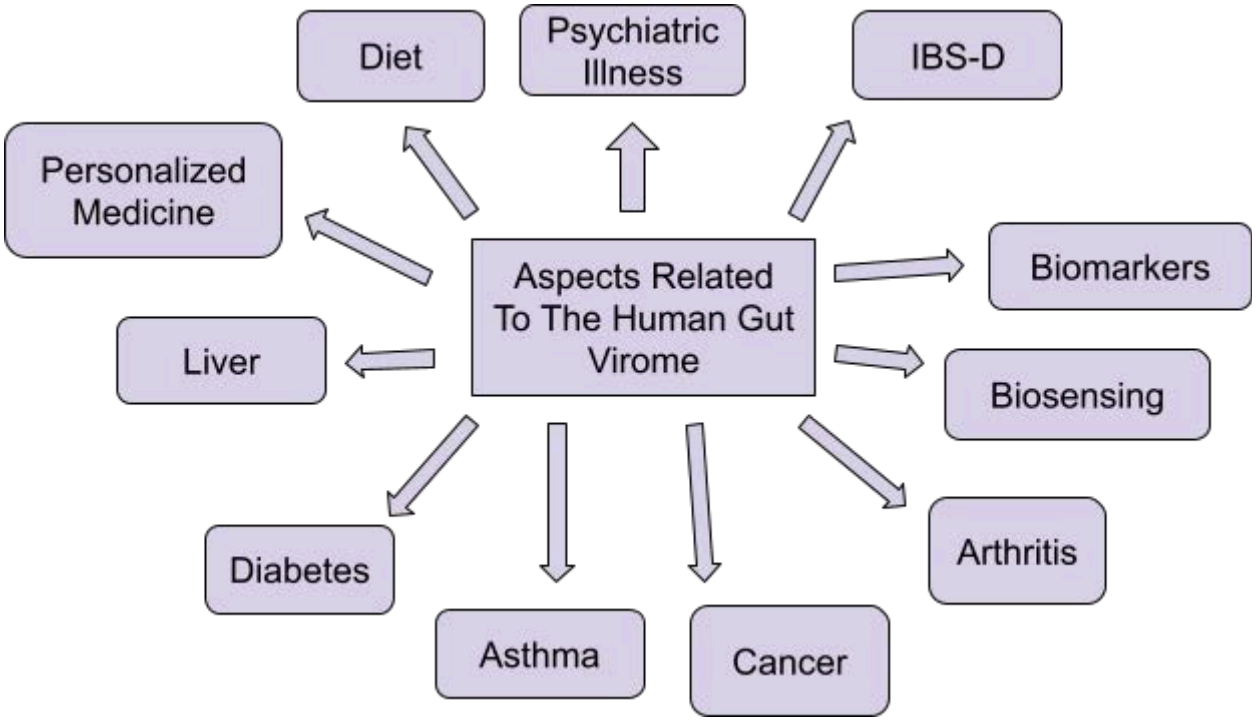


Figure 1: Aspects Related to The Human Gut Virome. This figure represents the different aspects that are related to the human gut virome, including; diet, psychiatric illness, IBS-D, biomarkers from the virome, biosensing using the virome, arthritis, cancer, asthma, diabetes, liver and personalised medicine.

Chapter 2

2. Role of the Human Gut Virome

The human gut virome forms an important, though traditionally neglected, part of the gut microbiome, and is largely composed of bacteriophages (viruses that infect bacterial hosts) but also includes eukaryotic viruses and endogenous retroviruses. To date, the bacterial microbiota has received considerable attention, however, it is emerging that the gut contains viruses that, like bacteria, have been identified as key in homeostasis and host health (Spencer, et al., 2022; Ogilvie & Jones, 2017). through bacterial populations through lytic and lysogenic cycles, favoring bacterial diversity, horizontal gene transfer, and shape the structure of the microbial communities (Townsend et al., 2021). These phages control bacterial function by transfection of

genes encoding the metabolic pathways, antibiotic resistance or virulence, in a process called "transduction" (Abeles & Pride, 2014).

The immune response to the virome is similarly influenced by the virome. Innate immune responses and the inflammatory or mucosal immunity may be modulated by some viruses, such as some eukaryotic viruses, that act through pattern recognition receptors (PRRs) (Focà et al., 2015b). Others promote immune tolerance by boosting regulatory T cells (Mukhopadhya et al., 2019). Through these interactions human virome can help maintain epithelial integrity and host defense from pathogens. It is not a mere set of parasitic entities, it is a whole active focused mechanism which contributes to establishing the host physiology and pathology.

Chapter 3

3. Influence of Genome, Age, Geography, and Other Factors on Virome Composition

The gut virome is deeply individualized and dynamic, under the influence of host genetics, age, diet, lifestyle and geography. According to Gregory et al. (2020a), the total virome diversity increases from early life to adult age and decreases in the elderly, with a peak in adulthood. This age-associated path is accompanied with bacterial diversity changes and immune system maturity implying a co-evolutionary association.

The virome also varies depending on geography and way of life. Zuo et al. (2020) and Rampelli et al. (2017) identified strong contrasts in the DNA virome between rural and urban populations. Non-industrialized region members (e.g., hunter-gatherers analogous to Hadza) had higher richness in phages including crAssphage and Microviridae, which also are linked to different bacterial hosts in high fiber, low processed food diets. Urban individuals, in contrast, had reduced viral diversity and a higher frequency of temperate phages, presumably as a result of antibiotic ingestion and the consumption of industrialised diets.

Also influential are host genetics and immune status. Both antiviral immunity and susceptibility to viral colonisation or persistence may be modulated by specific polymorphisms in immune genes (Wylie et al., 2012). Environmental factors, including antibiotics that modulate the bacterial hosts, also reshape the virome indirectly (Minot et al., 2013b). Accordingly, gut virome is influenced by both intrinsic (genetic and immunological) and extrinsic determinants (diet, geography, hygiene).

Chapter 4

4. Cross-Talk Between Viruses and Bacteria and the Role of Virus in the Microbiota

The interrelationship between the gut virome and bacteriome is complex, and are deeply intertwined in the gut microbiota, two communities that have co-evolved over ages. Most (76%) of the virome is represented by bacteriophages—mainly double-stranded DNA viruses, such as

Caudovirales and crAssphage, and serve as natural regulators of bacterial populations via both lytic infection and lysogeny (Pargin et al., 2023; Stern et al., 2019). They do so by fostering a multitude of microbes, and by resisting the takeover of one single taxon of bacteria—a concept called the "kill-the-winner" model. By lysogeny, the phages are able to insert into their bacterial hosts' genomes as prophages, providing advantages to the host such as toxin production, increased metabolic capabilities, or resistance to antibiotics, which can affect the host-pathogen relationship (Li et al., 2022).

The virome extends beyond bacteriophages and includes eukaryotic viruses such as members of Anelloviridae or Astroviridae as well as endogenous retroviruses. Some of these viruses are present asymptomatically in the healthy host and may contribute to immune training and epithelial integrity. Others may become pathological under certain conditions, e.g., immunosuppression. Additionally, viruses may also directly interact with host cells by: penetrating the epithelia barrier by increasing immune receptors and regulating inflammation (Cao et al., 2022). Therefore, viruses are not passive inhabitants but key components of the gut microbiota, and their functions include maintaining ecological balance between microbes, gene transfer among microorganisms, effects on immunity, and resistance to diseases (Tiamani et al., 2022). This emphasizes the need of including the virome as a part of the microbial ecosystem when studying it in clinical or research settings.

Chapter 5

5. Advantages of a Balanced Virome

A healthy gut virome promotes microbial diversity, immune homeostasis, and resistance to pathogens. For example, some phages like crAssphage contribute to user-level ecology and are required for Bacteroides to produce prebiotic short-chain fatty acids (SCFA) that protect the colon epithelium (Townsend et al., 2021). Through the suppression of pathobiont overgrowth, the virome serves as a brake on the development of inflammatory maladies (e.g., IBD, metabolic syndrome).

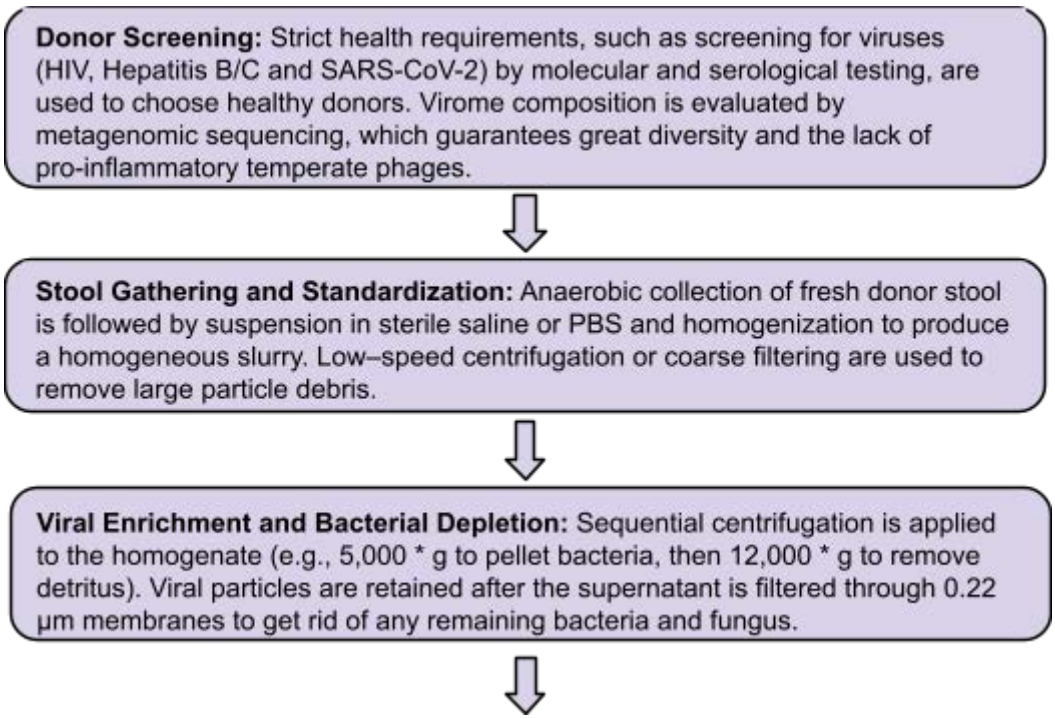
Moreover, phages also have potential applications for therapeutic purposes. Phage therapy is now being considered as an alternative to antibiotics in antibiotic-resistant infections. Specific phage cocktails can kill harmful bacteria while sparing good bacteria—in which way the good bacteria may not be targeted with antibiotics (Pavia et al., 2023).

Besides, some eukaryotic viruses also serve as immune modulators. For example, Anelloviruses have been linked to immune maturation in early life (Wylie et al., 2012). These results place the virome as a potential partner for health management and precision therapies.

Chapter 6

6. Inflammatory Bowel Disease (IBD-D) and Dysbiosis of Gut Virome

The gut virome, as part of the enteric microbiome, has been recently found to be a critical regulator in the development of IBD, which includes CD and UC. Recent metagenomic studies have shown an increase in abundance of Caudovirales, an order of tailed dsDNA bacteriophages but a decrease in general viral diversity and richness in individuals with IBD (Tun et al., 2023; Wu et al., 2025). This imbalance indicates a drift from a neutral viral ecology to a pro-inflammatory loss of balance with bacteria. Crucially, the increase in phage predation seems to rather selectively affect health promoting microbes. For instance, in both UC and CD, level of Faecalibacterium prausnitzii, a pivotal anti-inflammatory commensal of the Firmicutes phylum has shown to decrease with its phages increased in abundance, indicating targeted phage-mediated loss (Wu et al., 2025). Supporting this, Sinha et al. (2022) reported increased inflammation and altered host microbiome profile in response to fecal virome transplants from UC patients in a mouse model, which indicate the causal predictive role of virome alteration. Bacteriophages are the most abundant, but eukaryotic viruses such as Anelloviridae, Hepeviridae, and Orthohepadnaviridae have also been implicated in early disease progression, due to their capacity to interact directly with gut epithelial and immune cells (Tun et al., 2023). Rather, identifying an IBD "universal" virome signature has been difficult due to variations across individuals, as demonstrated by Stockdale et al. (2023) state that interindividual virome variability can overshadow disease-specific viral signatures. Yet, among this heterogeneity, there is increasing evidence that virome dysbiosis—specifically Caudovirales expansion and eukaryotic virus activity—is an underlying feature of IBD pathophysiology, interacting closely with both microbial composition and host immune responses.



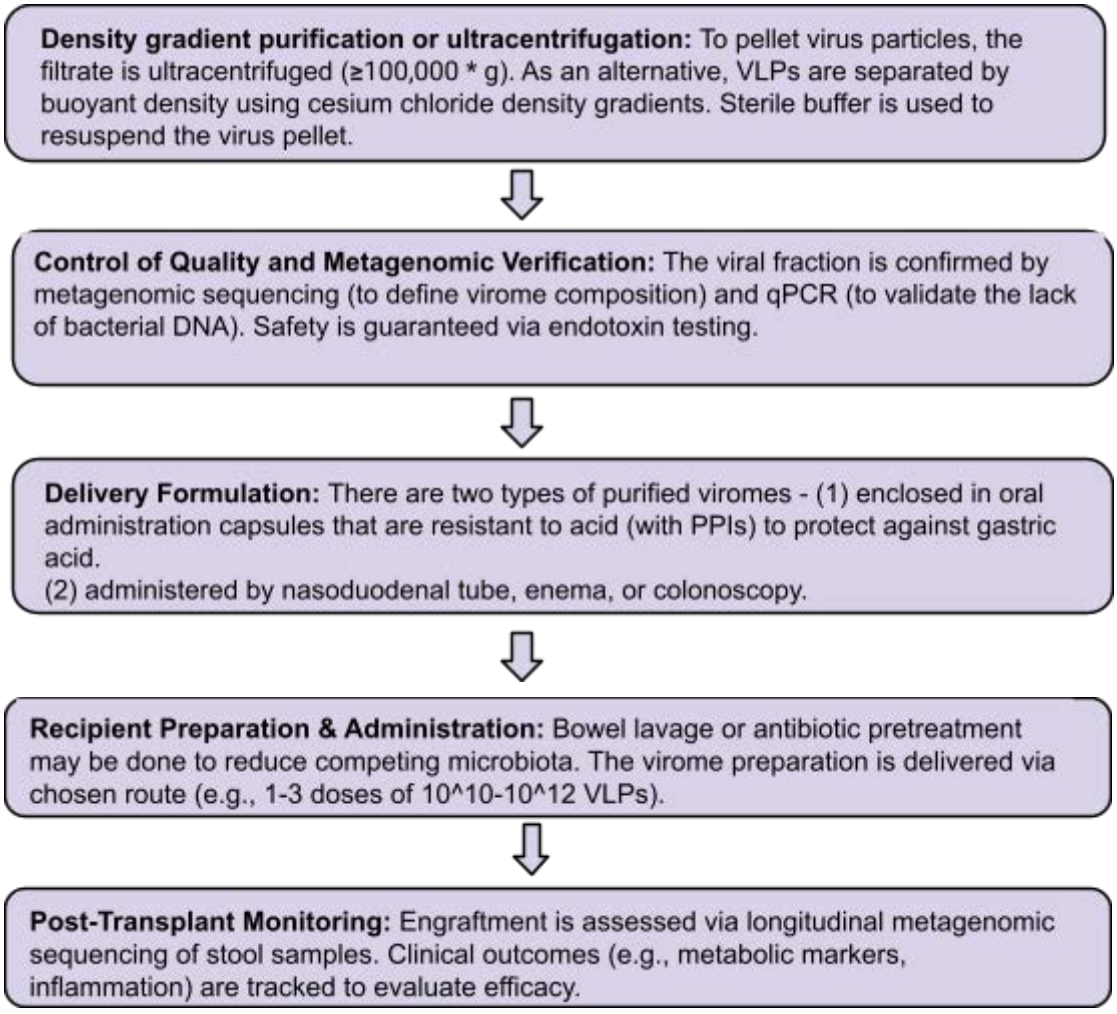


Figure 2: Fecal Virome Transplantation. This figure represents procedure steps required for a fecal virome transplantation (Rasmussen et al., 2020; Sinha et al, 2022).

Chapter 7

7. Virome Signatures and Mechanistic Insights in Ulcerative Colitis

Ulcerative colitis (UC) is now recognized as an emergent condition of specific viral signatures, in particular mucosa-associated virome. In UC, the metagenomics data have repeatedly revealed an enrichment of eukaryotic viruses, including Anelloviridae and Orthohepadnaviridae, as well as the emergence of Caudovirales bacteriophages, possibly all participants in the disease process. Notably, Massimino et al. (2023) observed a significant enrichment of the Orthohepadnavirus genus in mucosal samples of untreated UC patients. Functional analysis showed that these viruses had the capacity to cause intestinal inflammation in vivo, suggesting a direct involvement in the initiation of mucosal immune responses. In parallel, Zuo et al. (2019) found changes in mucosal viromes in patients with UC, enriched in Anelloviridae and with decreased viral

evenness, thus providing further support for the association between mucosal virome disturbance and immune dysfunction. Importantly, Jansen et al. (2023) also introduced a new categorization of virome community types that are associated with endoscopic severity, indicating the possibility of viral signatures as predictive markers of disease activity or response to treatment. These results are also consistent with loss of microbial diversity especially of beneficial species such as Firmicutes and Bacteroidetes as a result of elevated pressure of bacteriophages (Wu et al., 2025). Moreover, Focà et al. (2015) also had reported that the virome-induced mounting of the epithelial stress could promote the amplification of inflammation via the innate immune signaling. Collectively, these findings establish the virome as a potential effector of UC via direct immune activation and indirect microbiota reformation.

Chapter 8

8. Changes in the Virome and Their Impact on the Treatment of Crohn's Disease

CD displays a unique virome profile despite sharing major characteristics of dysbiosis with UC, that reflects its transmural inflammation and discrete nature. In particular, Pérez-Brocal et al. (2015) one of the first large virome studies to date in patients with CD demonstrated a significant enrichment of Caudovirales and Siphoviridae in active disease and decrease in commensal viral taxa such as Microviridae, which are frequently ascribed to gut homeostasis. Interestingly, these changes were found to be dynamic with respect to treatment, suggesting virome composition is both a marker and effector of disease state. The study also emphasized possible virus–bacteria co-interactions, in relation to, especially, expanded phages with reduced populations of Clostridiales and Ruminococcaceae, which are the major producers of the short-chain fatty acids necessary for gut health. Additionally, Wu et al. (2025) identified higher abundance of Hepeviridae (but lower Virgaviridae) in CD patients diagnosed early on the basis of mucosal biopsies, which supports the involvement of eukaryotic viruses in modulating mucosal immunity. These changes are in agreement with the observation of Tun et al. (2023), who suggested that the relative abundance of certain phages might influence the anti-inflammatory barrier effect of their host bacteria. That viral dynamics do change in response to treatment and co-vary with bacterial communities adds to their appeal beyond pathogenesis, as non-invasive biomarkers or therapeutic targets. In contrast to UC, where mucosal virome changes predominate, in CD, more profound viral infiltration and effect may be operating at a deeper, systemic level, providing an alternative perspective on virome-based diagnostics and interventions.

Chapter 9

9. Gut Virome and Type 1 Diabetes (T1D)

Recent studies have suggested that the gut viral community (virome) is a key environmental factor influencing T1D pathogenesis, especially at the early stages of immune development. In the should read "Studies in the ENDIA cohort (Kim et al., 2019) have also found that pregnant

women with T1D demonstrate a unique virome in the gut, with disrupted quantities of Picobirnaviridae and Anelloviridae, which could affect vertical viral transmission and immune priming in utero. Similarly, Zhao et al. (2017) performed longitudinal metagenomic analyses in genetically at-risk children and found that changes in the virome, increased presence of enterovirus and decreased diversity of Microviridae in particular, preceded appearance of islet autoantibodies and could be causative. The Picornaviridae family, in particular enteroviruses, especially Coxsackievirus B, have been speculated to trigger β-cell autoimmunity through means of molecular mimicry, bystander activation, or chronic infection, although findings are conflicting between cohorts. Of note, T1D related gut virome modifications are frequently associated with loss of bacteriophage diversity, mainly crAssphage and Siphoviridae, a dynamic that can destabilize the microbial balance and create a proinflammatory gut environment (Fang & Ning, 2024). This is corroborated by the Poulsen et al. (2024), found in patients with latent autoimmune diabetes in adults (LADA), also virome alterations different from those in classic T1D and T2D, indicating that a viral signature may differentiate between the (auto)immune diabetes types. In addition, the virome could interact with host genetics, for example-M Kim et al. (2019b) noted enhanced virome perturbations in HLA risk allele carrying women, indicating gene-environment interactions. While the causative role of the virome in T1D is still being investigated, early-life exposure to a range of viruses – both eukaryotic and bacteriophage-based – appears to act as a priming event for imbalances in immune homeostasis, and thus may provide early targets for the discovery of biomarkers or the development of interventions that modulate the virome.

Chapter 10

10. Changes in T2DM and Obesity

Unlike Type 1 Diabetes, Type 2 Diabetes (T2D) and obesity are characterized more by metabolic perturbation, and recent work identifies the gut virome as a major arbiter of microbial and immune crosstalk in these conditions. Several large-scale metagenomics studies have revealed a decreased richness and diversity in virome of individuals with T2D and obesity, associated with an enrichment of a few bacteriophage families like Caudovirales, Siphoviridae and Myoviridae (Yang et al., 2021; Fan et al., 2023). In particular, Ma et al. (2018) showed that signature of gut phages—enrichment in Lactococcus phages and depletion in Bacteroides phages—are positively associated with a number of host glycemic markers, such as HbA1c, indicating phage participation in shaping dysbiosis in association with glucose intolerance. Similarly, Rasmussen et al. (2020) demonstrated that fecal virome transplantation (FVT) reduced diabetes burden and insulin sensitivity in obese diabetic mice compared to conventional fecal microbiota transplantation. This implies that virome-targeting could be a more selective approach to microbial therapeutics. Furthermore, Kriti et al. (2025) broadened the horizon by pointing out the mycobiome-virome axis, suggesting that increased Candida abundance and entwined viral perturbations may contribute to mucosal inflammation and insulin resistance. These changes are

not universal; Wu et al. (2024) identified that the virome changes at early pregnancy predicted the onset of gestational diabetes mellitus (GDM), suggesting predictive, preclinical virome signature. Finally, Yang (n.d.) suggested a model in which the virome impacts bile acid metabolism, gut barrier integrity, and Toll-like receptor (TLR) signaling to establish a mechanistic link between the virome and metabolic disease. Taken together, these results depict the gut virome as a driver rather than a passenger in T2D and obesity pathogenesis, providing opportunities for early diagnostics, personalized medicine, and non-invasive metabolic manipulation by phage therapy or virome shaping.

Chapter 11

11. Effect on Diet

The human gut virome, which consists primarily of bacteriophages, is a key mediator of bacterial communities, immune function and gut homeostasis. The diet is the major environmental factor that can modulate this virome beneficially and negatively. Minot et al. (2011) presented initial evidence of a strong individual signature as well as rapid satiric response of the gut virome to diet. Their long-term study showed that as short term dietary changes occurred (for example, a shift from a low-fat, plant- to a high-fat, Western-type diet), large shifts in the abundance of phage families (such as Myoviridae, Siphoviridae (both within the order Caudovirales)) and the host microbiota were observed. High dietary fat consumption, particularly in the form of saturated fat, has been linked to the expansion of phages that infect beneficial Firmicutes, including Faecalibacterium prausnitzii, an anti-inflammatory commensal. Dysregulation or loss of such bacteria–phage interactions could lead to a microenvironment that supports inflammation and metabolic imbalances.

Echoing this more, Zhao and Wang (2024) described the impact of high fat and high sugar diets on gut viral communities and suggest these diets reduce overall levels of viral diversity whilst enhancing viral-bacterial co-occurrences associated with dysbiosis. These encounters are frequently followed by blooms of phages which lyse keystone bacteria, enabling pathogenic or opportunistic organisms like Escherichia coli or Clostridioides difficult to outcompete. This is especially true in a Western diet high in animal fats, sugar and processed food and low in fiber. The reduced availability of fermentable fibers also limits the generation of SCFAs by gut bacteria, which play a critical role in gut barrier function and viral-bacterial interactions.

The effect of a GFD on the virome may be more nuanced. Garmaeva et al. (2021), a significant decrease in crAss-like phages that infect Bacteroides spp., was observed in patients with gluten sensitivity or CD on a GFD. Although these phages are present in high abundance in non-gluten-sensitive guts, their higher prevalence in gluten-sensitive individuals is linked to inflammation. Therefore, a GFD in these cases may promote mucosal healing by reintroducing

homeostasis in the gut virome and reversing phage-driven microbial imbalances. But in non-sensitive people, cutting out gluten — especially without adding back in fiber-rich substitutes — lowers microbial and viral diversity. This loss can potentially compromise gut resilience as numbers of lytic and temperate phages contributing to preventing bacterial overgrowth and equilibrium are reduced.

Complementing macronutrients, exposure to foreign environmental viruses influences gut virome composition. Park et al. (2025) showed that the virome of the phyllosphere (the complement of viruses on fresh produce such as lettuce and spinach) can be translocated into the human gut. These comprise numerous phages from the Microviridae and Caudovirales that could be quite capable of engaging the resident gut flora. Though many such elements are benign or beneficial, some may bear mobile genetic elements associated with bacterial virulence and antibiotic resistance. The significance of eating raw, uncooked veggies is not just nutritional, it's microbial and viral as well.

Also, Zhao et al. (2024) and Garmaeva et al. (2021) highlight that various polyphenols in diet (such as found in fruits, legumes, and vegetables) are able to stimulate growth for bacterial species carrying temperate phages that help stabilize the virome, serving to ameliorate virome stability in adverse conditions of distress the host can experience. This synergy assists in preserving diversity (to some extent) and can suppress inflammation. Conversely the reduced polyphenol, high-fat diets tend to push the virome composition towards a context more lytic and less stable, that correlates with the chronic inflammation and metabolic disruption.

Virome composition is also indirectly associated with the larger food Georgia Archive environment, which is linked to food processing, nutrient density and hygiene. Story of the Research Del Carmen Mondragon Portocarrero and Lopez (2024) posit that by consuming ultra-processed foods that lack microbial and nutrient diversity, we might be losing the good viral taxa, while the consumption of a plant dominated, minimally processed diet enriches for a resilient and diverse virome.

In summary, dietary intervention, such as fat and fiber, gluten-free diet, and food-borne virus exposure, significantly alters the gut virome. Indeed, dietary patterns rich in plant-derived fibers, polyphenols, and natural complex microbiota are known to promote a diverse and stable virome, in turn promoting a healthy gut environment resistant to disease. High fat and low dietary fiber and extreme low-binding, or low residue, diets can shift the balance to allow virome-generated dysbiosis. Modifying our diet according to individual sensitivities, such as gluten intolerance, and attempting to maintain a high level of both microbial and viral diversity are therefore crucial for improving gut (and overall) health.

Chapter 12

12. Stress, Psychiatric Illness and Gut-Brain Axis

The human gut virome – composed of bacteriophages, eukaryotic viruses and endogenous viral elements – has taken a center stage as a key component in the gut microbiome, and has broad implications for host neurobiology. Though of course the microscopic life of bacteria has played star roles in the microbiome-to-brain geological age, studies as of late indicate that viruses, and notably phages (bacterial viruses), are also mediating drivers of microbial composition, immune function and central nervous system signaling. They are potentially permissive and the roles of these interactions are more and more established in psychiatric diseases, mood dysregulation, schizophrenia, and stress-related neuropathology through the microbiota-gut-brain axis (MGBA).

12.1 Virome Modulation Under Stress and Behavioral Effects

Stress is a well‑known gut microbial homeostasis disruptor, and the recent evidence links gut virome to this disruption. Ritz et al. (2024) also highlighted, in a murine model, the specific changes induced by chronic psychosocial stress in the gut virome, and in Caudovirales and Microviridae phage families. Interestingly, stressed mice showed lower levels of viral diversity and higher phage-to-bacterium ratios, reflecting a phage activity suggestive for bacteriolysis.

These distributions paralleled an enhancement of the gut permeability and the levels of pro-inflammatory cytokines (i.e., IL-6, TNFα) with the development of anxiety-like behaviors. Virome composition was highly correlated with alterations in Bacteroides, Akkermansia, and Lactobacillus bacterial taxa. The current study reports a potential mechanism for the dysregulation of bacterial communities and for the activation of mucosal immune response as well as of behavioral changes through the vagus nerve activation and the HPA axis stimulation in response to stress-induced viral shifts. Such results position phages upstream to stress-induce neuroimmune changes.

12.2 Virome Dysbiosis in Schizophrenia

The virome-bacteriome interface is most disrupted in schizophrenia. In a mass fecal metagenomic study, Tao et al. (2025) observed profound changes in DNA phages, particularly enrichment of Enterococcus- and Clostridium- infecting bacteriophages in schizophrenia. These alterations were associated with reduced microbial resilience and dysfunction of the GABAergic, glutamatergic, and tryptophan metabolism pathways–the critical mood and cognition regulators.

In particular, the disappearance of Lactobacillus and Faecalibacterium prausnitzii phages—concerned with short-chain fatty acid (SCFA) generation—was associated with disrupted gut-brain signaling. Furthermore, network fragmentation between phage and bacteria was evidence of mutual interference and promotion of pathobiont activity. Such microbial perturbations were associated with enhanced symptom severity and cognitive impairment in patients, hinting at a functional role of virome-mediated dysbiotic processes in the

pathophysiology of SCZ, likely by enhancing neuroinflammation and neurotransmission imbalance.

12.3 Mood Disorders and the Extended Perception of the Microbiome

Gut microbiome (GM) imbalances are considered to be closely linked with mood disorders, such as major depressive disorder (MDD) and bipolar disorder (BD). McGuinness et al. (2023) reason that while the bacteriome receives much of the spotlight, the virome is also an overlooked, but important, part of the system that mediates gut-brain communication. Although little direct data are available on virome shifts in mood disorders, phages may exer their action indirectly by controlling bacterial taxa crucial for the synthesis of neuroactive molecules.

For instance, phage-mediated lysis of Bifidobacterium, Lactobacillus, or Roseburia could lead to decreased production of gamma-aminobutyric acid (GABA), serotonin precursors, and butyrate, all linked to the regulation of mood. What's more, increased phage activity can also disturb microbial networks and provoke proinflammatory signaling, the latter of which is known to be elevated in depressive and anxiety states. The authors recommend incorporating a broader virome analysis into clinical mood disorder models to achieve an integrated view of the complete contribution of the microbiota to neurotransmitter synthesis, stress reaction, and affective regulation.

12.4 Gulf War Illness: Virome, Neuroinflammation, and Microglia Activation

In support of the notion that the virome also contributes to these impairments are findings from an inflammatory neuroimmune model. Seth et al. (2019) litrated DNA virome diversity in a mouse model of GWI and showed that distinct phage communities were associated with gut inflammation and microglial activation in the brain. Mice with higher viral richness, particularly of the Siphoviridae family, were associated with elevated TNF-α, IL-1β, and reactive astrocytosis.

Desulfovibrio- and Escherichia coli-targeting phages were linked with proinflammatory gut shifts and the elevation of neuronal toxicity markers. These data underscore the contribution of the virome to systemic neuroimmune priming, a process in which gut microbial signals such as viral ubiquitin metabolites or capsid proteins escape from the gut barrier and shape brain immune cells. The finding supports the concept that the virome may not only be involved in gut inflammation, but also participate in CNS pathologies associated with neurobehavioral disorder.

12.5 Stress, Viral Reactivation, and Collateral Diseases

The virome's reaction to stress isn't confined to the intestines. Talarico et al. (2024) summarized how long-term mental stress that is also chronically occurring, the immune system in the gut is damaged and reactivation of dormant viruses is enabled, such as Anelloviridae, Herpesviridae,

and Adenoviridae. These latent viruses can become reactively active, causing low-grade systemic inflammation, enhanced viral shedding, and the loss of epithelial barrier integrity. Suppressing secretory IgA (sIgA) and type I IFN responses due to stress makes our gut susceptible to viral penetration and gut microflora passage.

The presence of such viral reactivation, especially in patients who are immune-compromised or under high levels of stress, could help to explain previously reported associations between chronic stress and exacerbation of psychiatric symptoms. The authors indicate that stress-induced viral dynamics may mediate disease exacerbations in depression, anxiety, and neurodegenerative conditions, and that the gut virome represents a molecular bridge between the psychosocial stress system and systemic immune function.

12.6 The VIROME in Psychiatry – An opportunity which is passed?

Despite an increasing amount of evidence, the virome is still underrepresented in psychiatry. Yolken et al. (2021) highlighted connections between viruses and schizophrenia, bipolar disorder, and major depression, but noted that the majority of large psychiatric studies were conducted without viral sequencing. For example, previous investigations linked Herpes simplex virus (HSV) and Borna disease virus (BDV) with psychiatric complaints. They argue for the standard inclusion of virome profiling for psychiatric cohorts, and they posit that chronic viral infection, reactivation, or virome-bacteriome imbalance might be biomarkers or even treatment targets in neuropsychiatric disease.

Chapter 13

13. Infants' Gut Virome Linked to Asthma Risk

The gut virome, which is predominantly bacteriophage, is essential for the early establishment of the immune system with onward implications for respiratory health. Rodríguez et al. (2023) have shown that the composition of the infant gut virome is strongly correlated with risk of developing asthma by the preschool age—independently of gut bacteria. Babies who did not go on to get asthma had more phages from the Caudovirales order, which are believed to stabilize the bacterial communities that promote a tolerant immune system. Such phages could be affecting the gut microbiome in a manner conducive to maintaining a balance between Th1 and Th2, which helps prevent the development of chronic airway inflammation.

This result aligns with the proposed concept of the gut–lung axis, in which the immune cells and cytokines acting on respiratory tissues are influenced by gut microbial and viral communities. Viral manipulation of the gut microbiota could change the generation of immune-regulatory products, like SCFAs, which circulate in systemic blood and contribute to lung immunity.

Chapter 14

14. Allergy and Type 2 Inflammation by the Virome

In allergic diseases, such as asthma, the role of the virome in immune dysregulation is gaining attention. Mageiros et al. (2023) referred to the virome as a "nascent, ineffable player" in allergic disease but noted that discrete viral profiles can drive type 2 inflammation, a key feature of allergic asthma. Some components of the virus can lead to an epithelial disruption or deviation of the immune response towards a Th2 response with high production of cytokines like interleukin (IL)-4, IL-5, and IL-13. The process may be impaired in individuals with asthma leading to reduced protective antiviral immunity.

The influence of the virome is present in mucosal surfaces as well as systemic immune cells, and its breakdown can drive the immune landscape toward hyperreactivity. This has significantly increased the complexity of our concepts of asthma etiology, which has historically focused on allergens, genetics, and bacterial dysbiosis.

Chapter 15

15. Anelloviruses and Immunity Development in Early Life

Freer et al. (2018) addressed anelloviruses, a predominant element in the human virome present in almost all persons but at a particularly high frequency in those with immature or dysregulated immune systems. Early in life, when immune pathways are not yet established, the high prevalence of anelloviruses may indicate, or even cause, susceptibility to respiratory disorders such as asthma. High anellovirus loads are associated with abnormal cytokine signaling, impaired interferon production, and increased wheezing and viral respiratory infections.

Since anelloviruses are noninfectious but immunogenic, they may be good indicators of immune dysfunction or inflammation in children. Their relationships with host and (microbial) housemates imply they may play a role in moulding the developmental course of immune tolerance and responsiveness, the twin cornerstones of risk of allergic disease.

Chapter 16

16. Gut Virome Alterations in COPD

In addition to early-life asthma, perturbations in gut virome composition have been reported in adults with chronic obstructive pulmonary disease (COPD). Liu et al. (2024) found that patients with COPD had significantly lower gut virome richness and diversity, accompanied with distinct bacteriophage composition. These virome signatures were associated with changes in the bacterial landscape and on systemic inflammation, suggesting that gut virome dysbiosis may be associated with immune perturbation in COPD.

A subset of the reduced phage lineages in COPD patients associated with bacteria that produce the anti-inflammatory metabolite SCFAs. Loss of these phages might disrupt microbial communities, decrease metabolite levels, and lead to intestinal permeability, that can facilitate for translocation of pro-inflammatory molecules to the blood district and exacerbate lung inflammation. These results shed light on a potential mechanism underlying how perturbation of the gut virome is associated with age‐related exacerbation of respiratory disease progression.

Although the age of onset and clinical manifestations of asthma and COPD are variable, the gut virome seems to modulate host immune responses via common pathways in both conditions as well. These comprise viral control of bacterial colonization, alterations in cytokine and interferon signalling, and systemic immune activation. Phage-bacteria interactions and virome immune triggers might therefore constitute shared molecular underpinnings of gut virome diversity and perinatal respiratory disease pathogenesis.

Chapter 17

17. The Relationship Between The Human Gut Virome and Liver

Bacteriophages which infect bacteria are dominant members of the human gut virome and they have an important role in gut microbial homeostasis and the modulation of liver immunity via the gut-liver axis. The gut and liver communicate through the portal vein, by which metabolics products of bacteria, bacterial components, and viral particles can directly affect hepatic function. The dysbiosis of gut virome has been linked to the development or progression of a spectrum of liver disease such as non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease (ALD) and cirrhosis (Hsu et al., 2021). Gut-associated bacteriophages can shape gut bacterial populations by lysing certain bacteria or by transduction to influence HGT thereby affecting the microbial production of metabolites including SCFAs and bile acids. These metabolites modulate liver immunity, inflammation, and metabolism. For example, an unbalanced abundance in phages may cause overproliferation of pathogenic bacteria, resulting in an increase in gut permeability that permits bacterial endotoxins such as lipopolysaccharide (LPS) to reach the liver, which in turn causes inflammation and fibrosis (Matthijnssens et al., 2018).

Recent studies have suggested that phage therapy may be a potential treatment option for liver diseases due to its ability to selectively remove pathogenic bacteria and leave beneficial microbiota unaffected. Hsu et al. (2021) emphasize that phages that diminish pathogenic bacteria (such as Enterococcus faecalis) can alleviate alcoholic liver injury in mice, implying that the virome has applications in clinic. Moreover, the gut virome directly communicates with the host immune system, thereby modulating the generation of antiviral interferons and regulatory T cells associated with liver inflammation and fibrosis progression. In turn, the influence of the virome

on bacterial diversity also has consequences for the metabolism of bile acids – crucial for liver functioning and lipid homeostasis (Matthijnssens et al., 2018). Collectively, the gut virome is a critical mediator of the gut-liver axis and insight into its function creates new therapeutic opportunities for liver diseases using microbiome-targeted approaches, including phage-based therapies and probiotics. Prospective studies are needed to elucidate the contribution of certain viral communities to liver disease and if and how manipulation of the virome can restore microbial balance and maintain liver homeostasis.

Chapter 18

18. The Gut Virome in Osteoarthritis and Gouty Arthritis:

Chen et al. (2024), gut virome (bacteriophages+eukaryotic virus) plays two different roles for innate immunity-based host pathogenesis of osteoarthritis (OA) and gouty arthritis (GA). Based on metagenomic sequencing of fecal samples obtained from OA, GA and healthy controls, the study shows that both OA and GA patients display clear differences in viral community diversity, composition and function compared to healthy individuals. Interestingly, OA patients had a lower diversity of gut viruses and were enriched with bacteriophages targeting particular bacterial genera involved in inflammation and joint degradation, such as Prevotella and Bacteroides. This indicates that the gut homeostasis might be disturbed by phage-mediated modulation of the bacterial population which can provoke systemic inflammation through microbial metabolites (e.g., lipopolysaccharides) as it can lead to aggravation of joint tissue damage.

In contrast, GA patients had distinct virome types with high abundances of Caudovirales bacteriophages, and higher content of viruses targeting Streptococcus and Lactobacillus. These changes were associated with hyperuricemia—a signature of GA; thus, suggesting that this viral-bacterial interaction may have an impact on purine metabolism and uric acid precipitation. The study also highlighted dysregulated viral functional pathways in OA and GA: OA viromes were enriched for genes from biofilm formation and antibiotic resistance; which may contribute to chronic low-grade inflammation; while GA viromes displayed disturbances in nucleotide and carbohydrate metabolism pathways, corresponding to metabolic dysregulation in gout.

Importantly, the authors suggest that the gut virome is involved in arthritis pathogenesis through immune modulation. Phage-mediated lysis of bacteria could result in the release of bacterial DNA and peptidoglycans that subsequently activate toll-like receptors (TLRs) and the inflammasomes (e.g., NLRP3), and contribute to IL-1β-driven inflammation at the joint level. These results place the gut virome as a disease-specific biomarker and target: despite clinical judiciary OA versus GA, both are bound together by common theme of virome-driven gut dysbiosis that perturbs immune-metabolic axes. Whether virome modulation (eg, phage therapy)

might reset microbial composition and alleviate arthritis progression needs to be addressed in the future.

Chapter 19

19. Role in Cystic Fibrosis

In cystic fibrosis (CF), the malfunction of the CFTR gene not only impairs mucus production in the lungs, but also in the gastrointestinal (GI) tract, creating a specialized microenvironment that drastically changes the character of the gut microbiome and its associated virome (viral community, comprised mainly of bacteriophages). The study by Coffey et al. (2020) found that children with CF show a reduced diversity of the gut virome compared with healthy controls, characterized by lower levels of beneficial bacteriophages, against Bacteroidetes, and higher proportions of phages that infect Proteobacteria (e.g., Escherichia and Klebsiella). This transition furthers gut dysbiosis by allowing the prevalence of pathogenic strains to dominate when regulatory phage are eliminated. The viscous mucus in the CF gut also makes these bacteria stick together, which contributes to their ability to become more or less immobilized in the intestines and greatly increases the potential for bacterial overgrowth and intestinal inflammation.

The effects are not limited to the gut: bacterial toxins (eg, LPS) translocate through the leaky bowel barrier into the systemic circulation, resulting in systemic inflammatory response that may exacerbate CF lung disease—a concept that is tied to the gut–lung axis. Moreover, the dysregulated virome is unable to properly "teach" the immune system, probably leading to responses to infections becoming wrong. Indeed, the characteristic signature of the CF virome, e.g., the enrichment of Enterobacteriaceae-targeting phages, might be used as a marker of the disease severity or preemptive indicator of exacerbations.

Chapter 20

20. Phages as Health and Disease Biomarkers

The human gut virome, and in particular bacteriophages, offer great potential as a reservoir of non-invasive biomarkers of health and disease. According to Bakhshinejad & Ghiasvand (2017), phages are persistent, plentiful and highly specific to their bacterial hosts, suggested to be good candidates for diagnostic and prognostic purposes. They are representative of alterations in the microbiota (dysbiosis) and can indicate possible illness before developing a clinical syndrome. For instance, alterations in populations of Caudovirales (tailed phages) and Microviridae (small circular DNA phages) have been linked to inflammatory bowel disease (IBD), obesity and colorectal cancer. As previously mentioned, in CF, phage profiles may have been able to

differentiate disease severity or aid in the prediction of pulmonary exacerbations through studies of organism-specific phages (e.g., those that infected Pseudomonas).

In addition to diagnostics, phage biomarkers could even direct personalized therapies. If a patient's gut is dominated by Enterobacteriaceae-infecting phages, for example, they might be given targeted phage therapies to fight antibiotic-resistant infections. Conversely, reductions in phages that control beneficial bacteria (e.g., Bacteroidetes) may be indicative for the requirement of probiotic and phage interventions. Recent metagenomic sequencing also permits rapid profiling of the virome, but questions still surround the standardization of methods and the association between specific phages and clinical endpoints. Research in the future should examine longitudinal studies to demonstrate that these phage markers are true and can be combined with immune and host metabolic data for personalized medicine.

Chapter 21

21. Personalized Medicine and the Human Gut Virome

The human Gut virome which contains numerous bacteriophages and eukaryotic viruses is an emergent contributor to health and disease and raises potential new options for personalized medicine. The virome is a dynamic and highly personalized entity compared to the bacterial microbiome and it can make an attractive target for specific therapeutic approach (Lathakumari et al., 2025). As metagenomic sequencing has advanced it has been discovered that the personal virome of each person is distinct and is shaped by genetics, dietary intake, and environmental exposures. This heterogeneity implies that therapeutic interventions targeting the gut virome may be personalized to maintain and restore microbial equilibrium in diseases such as IBD, metabolic disorders, and liver diseases.

Phage therapy – or how to use bacteriophages to treat bacterial infections "One of the most interesting virome-based personalized medicine applications is phage therapy, which consists in using … bacteriophages to kill pathogenic bacteria without affecting commensals [beneficial micro-organisms]. For instance, patients with antibiotic-resistant infections or gut dysbiosis-related diseases could be prescribed personalized phage cocktails to clear harmful bacteria such as Clostridioides difficile and Escherichia coli but without affecting commensals (Lathakumari et al., 2025). Furthermore, the gut virome interacts with the immune system of the host, thereby modulating inflammation and mucosal immune responses. Based on a patient's virome, clinicians could be able to predict disease susceptibility and be empowered to create precision treatments, for example, immune-modulating therapies for autoimmune disease or viral-based probiotics to improve gut barrier function.

And the virome's ability to facilitate such gene transfer among bacteria — called horizontal gene transfer — can be exploited to genetically engineer medical microbes. "Synthetic biology techniques might be used to introduce engineered phages to target gut bacteria, to underpin such alternative therapeutic approaches," the authors suggested, adding that these phages could carry genes that encode for traits beneficial to gut bacteria, such as greater capacity to produce anti-inflammatory metabolites or to degrade toxic substances. There are perspectives that the contribution of AI to the virome and vice versa might be important to develop predictive modeling to identify high-risk subjects and for fine-tuning of treatment protocols according to the viral signatures (Lathakumari et al., 2025).

However, several challenges still need to be addressed, such as the standardization of virome characterization and large clinical trials. Yet, as research continues, the gut virome may transform personalized medicine, realigning the way we approach healthcare towards highly personalized treatments that take into account the special interactions between viruses, bacteria, and human physiology.

Chapter 22

22. Challenges and Future Directions

Despite these revelations, there are some challenges for virome research. First, there is no such universal marker gene (comparable to bacterial 16S rRNA) which makes viral identification and classification notoriously problematic. The majority of gut-inhabiting viruses are not well-studied and belong to the category of "viral dark matter" (Li et al., 2022). Detection is slowly advancing through metagenomics, including long-read sequencing and analysis of CRISPR-spacers.

Second is that distinguishing resident and transient viruses is difficult. Viral populations are characterized by high turnover rates and short-term studies do not always capture stable virome patterns (Minot et al., 2012). Moreover, existing reference databases are heavily biased to the cultivable viruses, and largely ignore the unculturable vast virome (Beller & Matthijnssens, 2019).

From a clinical perspective, safety and regulatory challenges must be overcome before phage-based or virome-altering therapies are approved. Personalized strategies to target the viromes are required due to the patient to patient variability of viromes (Shkoporov et al., 2019). Synthetic biology and machine learning could enable the design of personalized phage therapies for individual microbiota and immune profiles.

An exciting line of investigation is the combination of virome data with multi-omics (metabolomics, transcriptomics, proteomics) to develop holistic models of health. These

integrated data may also provide insights into how phage-bacteria-host interactions inform clinical outcomes and the prediction of the disease onset or response to therapy.

Chapter 23

23. Conclusion

The gut virome, long a mysterious member of the human microbiome, has recently taken center stage in health and disease, with far reaching implications for immunology, gastroenterology and beyond. Its massive diversity, personalized character, and tunable responses to environmental stimuli, highlight it as a biomarker of illness as well as a druggable target. Studies have demonstrated the importance of interactions between phages and bacteria for microbial ecology and the impact these interactions can have on immune tolerance as well as a wide variety of pathologies - from chronic inflammation to cancer. For instance, virome-dysbiosis-driven diseases—e.g. enrichment of pro-inflammatory crAss-like phages in IBD or oncogenic viral strains in CRC—underscore its value as a diagnostic and intervention target.

Despite this progress, important deficiencies persist. The functional pathways that connect single viral taxa to disease phenotypes are far from clear, and the long-term consequences of virome manipulation (e.g., FVT or phage administration) require a step-change in their clinical validation. Furthermore, the interactions between the virome, mycobiome, and bacteriome complicate the picture, and there is a legitimate argument for multi-omics strategies to dissect the total influence. Future studies should focus on standardizing virome profiling procedures, longitudinal follow-up of virome evolution and mechanistic understanding of how viruses shape host pathways such as barrier integrity, cytokine signaling, and metabolite homeostasis. Additionally, the great majority of research concentrates on bacteriophages, disregarding the possible applications of eukaryotic viruses in disease (Pavia et al., 2023). There are also ethical concerns regarding unintentional horizontal gene transfer during therapeutics which linger (De Jonge et al., 2022)

The virome provides an unprecedented therapeutic potential. Phage-based personalized therapies may change the way antibiotic-resistant infections are treated, whereas dietary or probiotic approaches to select for beneficial viral communities could prevent or ameliorate chronic illnesses. Moreover, the potential of the virome for personalized medicine, with specific viral portraits used as therapeutic guidelines, is enormous. Better developments of curated databases may accelerate taxonomic resolution (Gregory et al., 2020). In addition to this, longitudinal studies tracking virome stability after fecal virome transplantation is required to evaluate durability (Zuo et al., 2020). The blending of virome data with proteomics and metabolomics may be allowed to bring to light links to host physiology (Cao et al., 2022). Lastly, clinical trials investigating engineered phage cocktails or dietary modulation answer may many unrequited questions (Lathakumari et al., 2025).

Taken together, the human gut virome is a frontier of microbiome science that connects microbial ecology with clinical medicine. As we disentangle its intricacies, the virome has the potential to be a centerpiece of next-generation diagnostics, therapeutics and preventive health regimens re-envisioning the way we address some of our most common and intractable diseases of the modern era.

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