Microbiome-Based Precision Medicine: Targeting Gut Health

Amatun Noor Prapty [1*] Willy Munyao [2]

Abstract

Precision medicine requires to optimize treatment efficacy by addressing individual variability in responses to medical interventions. The 2015 Precision Medicine Initiative laid the groundwork for developing innovative tools and fostering collaboration to enhance patient care. Among its critical areas of focus, the human microbiome has emerged as a pivotal determinant of health and disease, influencing physiological, neurological, and endocrine functions, as well as drug metabolism and disease progression. This review examines microbiome-based precision medicine strategies, including probiotics, dietary modifications, and fecal microbiota transplantation, emphasizing their potential to overcome the limitations of conventional one-size-fits-all approaches. Evidence demonstrates that personalized interventions tailored to individual microbiome profiles can significantly improve treatment outcomes and prevent chronic diseases. Case studies underscore the transformative potential of these therapies across various medical fields. However, challenges such as standardization, ethical considerations, and legal frameworks remain critical barriers to widespread adoption. Despite these hurdles, microbiome-based precision medicine represents a promising frontier in healthcare, offering specialized and effective therapeutic strategies. Future research must address these challenges to unlock the full potential of microbiome-informed approaches, advancing personalized care and improving patient outcomes.

Keywords: Gut Microbiota, Precision Medicine, Personalized Interventions, Microbiome.

Significance | Microbiome-based precision medicine enhances treatment efficacy and personalization, promising better patient outcomes and addressing conventional healthcare limitations.

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1. Introduction

The sequencing of the human genome in 2001 (Venter et al., 2001) marked a significant milestone in understanding the genetic basis of disease and revolutionized the application of DNA sequencing technology in patient care. Precision genomic medicine emerged from this progress, focusing on leveraging an individual's unique genome to inform treatment and care decisions by identifying genetic markers for disease (Guttmacher et al., 2012). A broader and more inclusive discipline, precision medicine integrates clinical data and genetic indicators with demographic, lifestyle, and medical history factors to customize therapeutic interventions.

While genomic medicine and precision medicine are often conflated, they differ in scope. Genomic medicine concentrates on genetic contributions to disease, rooted in the genome's role as a determinant of human uniqueness in the context of illness. In contrast, precision medicine extends beyond the genome to include downstream factors such as metabolic indicators, gene expression, and protein activity. Despite this broader approach, genomic data remains the most extensively utilized and has demonstrated remarkable success, particularly in cancer therapy (McCarthy et al., 2013; Garraway et al., 2013).

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Advances in genomic medicine have transformed cancer treatment, highlighting the potential of precision medicine even amidst challenges in implementation. The ultimate goal of precision medicine is to enhance disease diagnosis, reduce treatment-associated risks and side effects, and minimize instances of non-responsiveness to medication. Achieving these objectives promises to revolutionize healthcare delivery by transitioning from reactive, generalized treatments to cost-effective, preventive care tailored to the individual patient (Schork, 2015). This transformative potential underscores the importance of continued research and innovation in precision medicine to overcome current barriers and maximize its benefits.

2. The Microbiome as a Precision Medicine Frontier

This review focuses on integrating the human microbiome into precision medicine, a conceptually aligned yet more recent trend. The human microbiome is defined as "the ecological community of commensal, symbiotic, and pathogenic microorganisms that literally share our body space" (Lederberg & McCray, 2000). These microorganisms, primarily bacteria, fungi, viruses, and archaea, inhabit the gastrointestinal system and are sometimes considered a newly discovered organ due to their marginally higher prevalence than human cells in the body (Sender et al., 2016). However, unlike human cells and organs, the microbiome is far more dynamic and variable in composition and spatiotemporal dynamics. Thus, it is more accurate to view the microbiome as a "cloud" of genetic information accessory to the stable human genome (ElRakaiby et al., 2014).

The microbiome profoundly influences human physiology, affecting immunology (Surana & Kasper, 2014), neurology (Sampson & Mazmanian, 2015), endocrinology (Clarke et al., 2014), and, critically for precision medicine, disease states and clinical outcomes. Despite being a relatively young field, microbiome science is expanding rapidly, uncovering novel roles for this microbial ecosystem. These advancements have been propelled by the same sequencing technologies that enable personal genomics, with costs decreasing significantly (Lupski, 2010). Personal microbiome sequencing is now accessible to consumers through platforms such as American Gut (americangut.org) and uBiome (ubiome.com).

Microbiome analysis parallels genomic medicine in its reliance on sophisticated statistical and computational methods. However, unlike genetic traits, microbiome states can be rapidly altered (David et al., 2013) and are uniquely individualized, even among co-raised identical twins (Franzosa et al., 2015). This plasticity offers immense potential for personalized therapies. Nonetheless, the microbiome is highly complex, akin to any ecosystem, and achieving the full objectives of precision microbial medicine requires extensive research (Gilbert et al., 2016).

Despite these challenges, the microbiome is well-positioned to be integrated into precision medicine. Practical applications of microbiome-based therapies are on the horizon, supported by various complementary methods for testing and modifying the microbiome. These methods will be explored in detail in this review, with conceptual illustrations provided (Figure 1).

The diagram highlights techniques in precision microbiome medicine and their interactions:

a) Certain bacteria, such as those depicted in red, metabolize substances like cycasin into carcinogenic compounds like methylazoxymethanol (MAM) (Spatz et al., 1967). Metagenomic sequencing can identify the functional potential of these harmful microbes.

b) Three strategies (illustrated by green arrows) can target and eliminate harmful microorganisms without disrupting beneficial companion bacteria (depicted in blue). These include:

- Tailored antibiotics to eradicate specific pathogens while preserving commensal microbes.
- Prebiotic therapy to promote the growth of existing beneficial microbes.
- Probiotic therapy to introduce new beneficial microorganisms.

While probiotic and prebiotic therapies may not directly eliminate harmful bacteria, they can alter the gut environment to inhibit their growth (Schoeni & Wong, 1994). The choice of intervention depends on the specific microbial and host conditions, as well as the long-term impact on the microbiome.

This review demonstrates how these precision microbiome medicine techniques can be effectively integrated into clinical practice, paving the way for tailored therapeutic approaches that align with the broader goals of precision medicine.

3. Review of Microbiome Analysis Techniques

The application of precision medicine to the microbiome involves sophisticated tools like 16S rRNA sequencing and shotgun metagenomics. Both approaches begin with the extraction of microbial genomic DNA and are complementary in their scope. The 16S rRNA gene contains highly conserved regions that enable the use of nonspecific primers for bacteria, alongside hypervariable regions that allow species-level identification (Clarridge et al., 2014). Consequently, 16S rRNA amplicon sequencing is a robust method for classifying, identifying, and discovering microorganisms (Woo et al., 2018).

A typical 16S rRNA study aims to analyze differences in bacterial communities across samples to identify statistically significant correlations between microbiome composition and specific conditions. For instance, it has been used to examine differences in gut microbiomes between children born to obese mothers and those

born to non-obese mothers (Galley et al., 2014). Such studies have significantly advanced our understanding of the human microbiome, revealing its essential roles in both health and disease. Although bacterial research has historically focused on eradicating pathogens (Lederberg & McCray, 2000), precision medicine aims to identify both harmful bacteria and the broader ecological context of microbial communities, which may be equally critical.

3.1 Factors Influencing the Gut Microbiome

The composition and functionality of the gut microbiome are shaped by a wide range of factors, as illustrated in Figure 2. These factors include drug and alcohol use, physical activity, mental stress, and smoking, which collectively influence microbial diversity. Importantly, gut microbiota can modulate medication toxicity and efficacy, though the degree of this modulation varies widely between individuals, primarily due to the unique composition and functionality of each person's microbiome. The bioactivities of enzymes and the diversity of metabolites produced by gut microbes reflect the functional diversity of the microbiome in a scalable manner.

3.2 From Microbial Identification to Functional Potential

To move beyond bacterial identification and improve patient stratification, understanding the functional potential of the microbiome is crucial. Unlike 16S rRNA sequencing, which relies on amplifying a marker gene, shotgun metagenomics analyzes the entire genomic repertoire of a microbial community. This method enables researchers to assess not only the phylogeny of functional genes but also the metabolic and signaling potential of the microbiota by reconstructing genomes of unculturable organisms (Sangwan et al., 2016). These insights help reveal interactions between microbes and the host, as well as the microbiome's potential to influence disease states and clinical outcomes (Cardona et al., 2016).

Despite its advantages, shotgun metagenomics faces challenges, including higher costs, computational demands, and potential contamination from extraneous DNA (Thomas et al., 2012). Additionally, biases in data interpretation may favor culturable organisms, which could limit the method's applicability. Addressing these challenges is essential for scaling metagenomics to larger patient populations and fully integrating it into precision medicine.

3.3 The Dynamic Nature of the Microbiome

Both shotgun metagenomics and 16S rRNA sequencing have limitations in capturing the microbiome's fluid nature. Factors such as horizontal gene transfer, microbial evolution, and small differences in characterization make microbiome snapshots inherently crude (Jeffery et al., 2012). However, advancements in sequencing technologies and decreasing costs may enable time-series approaches, providing insights into dynamic ecological phenomena and microbial interactions previously inaccessible (Faust et al., 2015).

The microbiome also exhibits spatial heterogeneity within the gut, which can influence disease states and functionality (Donaldson et al., 2015). New sampling techniques, such as laser microdissection of colonic crypt mucus, show promise in overcoming these limitations by allowing researchers to analyze microbiota in specific gut regions with greater precision (Rowan et al., 2010).

As sequencing technologies evolve and costs continue to decline, the potential for microbiome-based precision medicine will expand significantly. Current tools like 16S rRNA sequencing and shotgun metagenomics are laying the groundwork for uncovering the microbiome's role in health and disease, but further advancements in technology, methodology, and computational analysis are needed to refine these approaches. The future of precision medicine lies in integrating dynamic, spatially resolved, and functionally insightful data, ultimately enabling personalized treatments that leverage the full complexity of the human microbiome.

4. Avenues Towards Microbiome-Based Precision Therapies

4.1 Microbiome-xenobiotic interactions

The role of genetic variations in drug metabolism has been known for decades. As early as 1957, researchers discovered that abnormalities in serum cholinesterase could lead to life-threatening reactions to certain anesthetics (Sultana et al., 2013). Such adverse drug reactions (ADRs) are a significant cause of patient non-compliance and therapy failure (Edwards et al., 2000), contributing to an estimated annual cost of $30 to $130 billion in the United States alone (Sultana et al., 2013). Reducing these side effects remains a critical goal of precision medicine.

A recent review on ADRs estimated that approximately 35% of these incidents involve drug-gene or drug-drug-gene interactions, particularly those associated with cytochrome P450 (CYP) variations, while others are idiosyncratic (Verbeurgt et al., 2014). CYP enzymes, regarded as the body's principal general-purpose drug metabolizers, are thought to mediate approximately 75% of all drug modifications in humans (Guengerich et al., 2018). However, the gastrointestinal microbiota also plays a pivotal role in biotransformation, particularly for compounds with low permeability and solubility (Rizkallah et al., 2012). The PharmacoMicrobiomics database currently identifies over 60 drugs that interact with the microbiome (Rizkallah et al., 2012). Given the vast potential for unique microbial metabolic transformations (Carmody et al., 2014), the number of microbiome-drug interactions is likely to surpass the comparatively limited human genetic interactions. This dynamic nature of microbial metabolism, driven by the microbiome's plasticity, underscores the need for patient-specific and temporally precise therapeutic strategies (Wilson et al., 2015).

The mechanisms of xenobiotic metabolism differ substantially between bacterial and human cells. In bacterial systems, reduction and hydrolysis are predominant, while human cells primarily employ oxidation and conjugation (Sousa et al., 2018). These differences are significant for drug metabolism, particularly for prodrugs—medications designed to be metabolized into pharmacologically active compounds after ingestion. Microbial metabolism can influence the activation of these prodrugs, thereby affecting therapeutic outcomes positively or negatively (Rautio et al., 2018). This interaction often manifests through alterations in a drug's bioavailability, a critical parameter for precise dosage predictions in precision medicine.

The microbiome's influence on drug efficacy and toxicity is well-documented. For instance, the hepatotoxicity of acetaminophen varies significantly across populations, partially due to microbial activity (Watkins et al., 2016). Certain bacteria, such as species within the genus Clostridium, produce p-cresol, which competes with acetaminophen as a substrate for the human liver enzyme SULT1A1, leading to an accumulation of the toxic metabolite NAPQI (Clayton et al., 2019).

Figure 3 illustrates the multifaceted interactions between gut microbiota and xenobiotics. Panel (A) highlights the effects of xenobiotics on gut microbiota composition, including inhibition, promotion, elimination, and colonization. Panel (B) emphasizes metabolism-related activities of the gut microbiota, such as enzyme synthesis for xenobiotic transformation (i), enterohepatic cycling of transformed xenobiotics (ii), and direct binding to xenobiotics, which reduces their absorption by the host (iii). Additionally, gut microbiota can modulate the immune response (iv), alter hepatic gene expression (v), compete for enzymes and drug transporters (vi), and act as intermediates in complex metabolic pathways (vii).

One significant challenge in pharmacology is the competition between bacterial metabolites and drugs for human enzyme modification (Swanson, 2015). Microbial metabolism can also produce harmful byproducts. For example, bacterial β-glucuronidase activity has been implicated in diarrhea caused by an anticancer camptothecin derivative (Viaud et al., 2013). Interestingly, metabolic variation can also occur at the strain level. In one case, a non-universal gene in Eggerthella lenta was found to inactivate digoxin, a drug with a narrow therapeutic index, where incorrect dosing can lead to severe toxicity. This highlights the need for further research into metagenomic diagnostics to mitigate unfavorable outcomes (Haiser et al., 2013).

Beyond metabolic pathways, microbiome-xenobiotic interactions can involve immunological and endocrine regulation. For instance, gut bacteria influence host immune responses (Shajib et al., 2015) and endocrine functions (Clarke et al., 2015), thereby complicating and expanding the scope of potential drug-microbiome interactions. Additionally, these interactions are often reciprocal: drugs can alter the microbiome, just as the microbiome influences drug metabolism. Antipsychotic medications, for example, not only modify the microbiota but also exhibit microbiome-dependent side effects (Davey et al., 2013).

While these complexities present challenges, they also suggest innovative strategies for precision medicine. By targeting the microbiome directly, therapeutic outcomes could be optimized in a microbiome-driven approach to drug design and application. Understanding these bidirectional interactions is key to advancing precision medicine and reducing the burden of ADRs.

4.2 Targeting the Microbiota: From Antibiotics to Precision Antimicrobials

Antibiotics provide a clear example of how medicine is already being used to directly affect the microbiota. While their primary purpose is to eradicate harmful bacteria, antibiotics exert broad effects on the microbiome, which may lead to unintended consequences. Among these, antibiotic-induced secondary infections are well-documented, with Clostridium difficile infections being a prominent example (Davey et al., 2013). Beyond these microbial consequences, antibiotics can also cause adverse effects in humans, such as the cardiotoxic responses associated with fluoroquinolones (Rubinstein, 2012) and the neuropsychiatric effects reported with this drug class (Galatti et al., 2015). Interestingly, some side effects of antibiotic use, such as decreased inflammation, can result from both unintentional shifts in microbial community composition and off-target effects of the drugs on human cells (Rubin et al., 2015).

Research in rodent models has demonstrated how antibiotics can alter physiological responses. For instance, broad-spectrum antibiotics reversed stress-induced elevations in circulating cytokines, highlighting the interplay between the microbiome, immune responses, and inflammation (Bailey et al., 2011). Notably, antibiotics are not the only medications that modulate the structure and function of microbial communities. Other drugs, which are not classified as antibiotics, are increasingly recognized for their ability to influence the microbiome (Wallace et al., 2013).

Although many perturbations of the microbiome are associated with poorer health outcomes, certain medications derive part of their therapeutic benefits from targeted modulation of the microbiome. These could be considered a type of selective antibiotic. Precision treatments that restructure microbial populations to optimize outcomes represent an intriguing avenue for medicine. Compared to conventional broad-spectrum antibiotics, pathogen-specific treatments hold the potential for significantly improved efficacy. Developing enzyme inhibitors or alternative antimicrobial compounds with species-specific activity is one promising strategy. For example, a drug targeting Streptococcus mutans has been developed, utilizing a fusion of a broad-spectrum antimicrobial peptide domain with a species-

specific targeting domain (Maurice et al., 2013). While effective, this peptide caused unexpected changes in the surrounding bacterial community, likely due to the structural and functional complexity of the oral microbiome, where S. mutans resides (Guo et al., 2015; Belda-Ferre et al., 2015). This underscores the need for careful evaluation of ecological impacts, even with targeted antibiotics.

An alternative approach involves targeting specific bacterial enzymes rather than killing bacteria outright. This strategy has the potential to address the dual challenges of antibiotic resistance and the unintended restructuring of microbial communities. For instance, in a multi-species model, targeted inhibition of bacterial trimethylamine (TMA) synthesis by 3,3-dimethyl-1-butanol (DMB), a structural analog of choline, successfully attenuated atherosclerosis in animals on a high-choline diet (Wang, 2015). Although subtle shifts in microbial composition were observed, this work highlights the dynamic nature of the microbiome and provides a foundation for microbiome-based therapies for Western diet-related diseases. Since the goal here is to globally reduce TMA production, a single-target approach is insufficient. However, precise, non-lethal drugs leveraging isozyme-specific inhibitors (Yao et al., 2016) could potentially be developed to minimize microbiota-drug interactions while selectively targeting pathogens. Additionally, such drugs could be engineered to have minimal bioavailability in humans, reducing the risk of systemic side effects.

Phage therapy offers another promising approach to targeted microbiome modulation. Though less common in the West, phage-based antimicrobials have been used successfully for nearly a century (Nobrega et al., 2015). Phages were independently discovered in England and France as a treatment for bacterial infections, such as cholera. Despite their efficacy, phage therapy never gained widespread use in the United States or Europe due to manufacturing challenges and the rise of antibiotics (Kutter et al., 2010). However, during World War II, scientists in the Soviet Union, particularly in Georgia, advanced phage therapy, applying it to manage gastrointestinal illnesses and further developing it during and after the Cold War (Summers et al., 2012).

The underlying principle of phage therapy lies in the specificity of phage-bacteria interactions. Each bacterial species or strain has unique cell membrane proteins and sugar complexes that phages can target (Koskella et al., 2013). By identifying the appropriate phage, it is possible to selectively eliminate a single bacterial species, enabling the precise redesign of a microbiome to enhance its functional characteristics.

Innovative approaches aim to leverage phage-targeting mechanisms to develop nanoparticles that mimic phages in their ability to selectively infect and eliminate bacterial cells. Such technologies, supported by recent findings from the commercial sector, could provide unprecedented control over the microbiome (Pers. Comm. Jeffrey Miller, UCLA). In the future, we may achieve precise manipulation of the microbiome to enhance health outcomes, ushering in a new era of microbiome-centered precision medicine.

4.3 Prebiotics: Enhancing Microbiome Function

An alternative to reducing harmful bacteria is to boost beneficial bacteria or improve microbiome function. This approach, commonly known as prebiotics, primarily involves non-digestible fiber compounds that stimulate the growth of beneficial taxa like Bifidobacterium. These bacteria produce short-chain fatty acids (SCFAs), such as propionate and butyrate, which have therapeutic potential for various ailments (Petschow et al., 2013; Candela et al., 2010). However, current prebiotics remain limited in scope, and expanding their definition is critical for advancing precision medicine.

As metagenomic and metabolomic technologies continue to reveal the metabolic potential of the microbiome—particularly across populations with diverse diets—new prebiotics targeting alternative beneficial bacteria and metabolic pathways are likely to emerge (O'Keefe et al., 2015; Preidis et al., 2019). These advancements could lead to the discovery of compounds that drive the microbiome toward favorable metabolic endpoints, broadening the therapeutic applications of prebiotics.

A more ambitious goal involves fine-tuning microbial interactions within the gut ecosystem. The microbiome produces various bioactive compounds essential for intercellular communication. Identifying those that beneficially alter microbial dynamics may yield novel prebiotic strategies (Garber, 2015). Unlike xenobiotic or microbiome-targeted drug metabolism, prebiotics leverage existing biological pathways, resulting in less disruption to the microbial community.

While achieving this level of precision may seem distant, advancing dynamical systems approaches to microbiome research could illuminate how targeted prebiotic interventions stabilize or gently perturb the microbiome in at-risk populations. This nuanced approach may prove vital for managing dysbiosis and maintaining microbial balance (Garber, 2014).

4.4 Probiotics and Gut Microbiota-Based Biomarkers in Precision Medicine

Probiotics, live bacteria administered for health benefits, represent one of the most direct methods to alter the microbiome. Élie Metchnikoff first proposed in 1907 that lactic acid-producing bacteria might colonize the gastrointestinal system and promote longevity (Gordon et al., 2018). While subsequent research has revealed that their benefits extend far beyond the production of a single metabolite, lactic acid bacteria, particularly those within the genus Lactobacillus, continue to dominate the field of probiotics (Bron et al., 2011). Advances in microbiology now suggest that other beneficial bacteria, potentially isolated from healthy

individuals, could also have significant therapeutic effects through diverse mechanisms (Belda-Ferre et al., 2012).

The specificity of probiotic applications has paved the way for precision probiotics tailored to individual needs. For example, devices capable of separating microorganisms based on their metabolic output are already in use, and researchers are actively identifying probiotic strains that produce bioactive compounds with medicinal potential (Gavrish et al., 2016; Strandwitz et al., 2015). Engineered probiotics are being developed to enhance resilience, broaden functionality, and expand therapeutic applications (Amalaradjou et al., 2013). Importantly, the effects of probiotics are influenced by interactions with the host's existing microbiota, genetics, and diet, necessitating accurate patient stratification to maximize therapeutic outcomes (Bron et al., 2011). Precision probiotics have demonstrated tangible success, such as improving resistance to Clostridium difficile infections (Buffie et al., 2014) and inhibiting hepatocellular carcinoma in mice (Li et al., 2016). However, their future success will rely on a deep understanding of the metagenomic potential and ecological interactions of probiotic strains.

Leveraging gut microbiota and its components—genes, enzymes, strains, species, and metabolites—as biomarkers offers immense potential for precision medicine. Enzymatic activity, in particular, serves as a practical biomarker due to its central role in drug metabolism and its impact on medication efficacy and toxicity. When enzymatic activity is difficult to measure directly, analyzing the genes encoding these enzymes provides an alternative.

Berberine, an alkaloid derived from plants like Coptis chinensis and Berberis vulgaris, is widely used in China to treat hypercholesterolemia and bacterial diarrhea (Ni et al., 2017). Despite its clinical benefits, berberine has low bioavailability, necessitating high doses that often lead to gastrointestinal side effects such as diarrhea and abdominal discomfort (Yue et al., 2019). Recent studies have identified nitroreductases, gut microbiota enzymes that convert berberine into dihydroberberine, a more absorbable form, significantly improving its bioavailability (Feng et al., 2015). Clinical data suggest a positive correlation between nitroreductase activity and berberine absorption, making this enzyme activity a promising biomarker for personalized berberine therapy in hyperlipidemia (Wang et al., 2017).

Digoxin, another example, highlights the complexity of gut microbiota-drug interactions. Decades ago, researchers discovered that Eggerthella lenta metabolizes digoxin into the inactive compound dihydrodigoxin (Haiser et al., 2013). However, variability in digoxin metabolism among individuals colonized with E. lenta revealed that bacterial abundance alone is insufficient to predict drug metabolism (Dubin et al., 2016). Recent research identified the "cardiac glycoside reductase" (cgr) operon in certain E. lenta strains as responsible for digoxin metabolism, suggesting that screening for these genes could predict drug response more accurately (Koppel et al., 2018).

While bacterial abundance may not always correlate with drug metabolism, it remains useful in certain contexts. For instance, tacrolimus, an immunosuppressant commonly used by renal transplant recipients, exhibits significant inter-patient variability in effectiveness and toxicity. High doses risk nephrotoxicity and neurotoxicity, while sub-therapeutic doses can lead to graft rejection (Weber et al., 2013). A study of kidney transplant patients found a significant correlation between tacrolimus dose adjustments and the presence of Faecalibacterium prausnitzii in the gut microbiota (Lee et al., 2018). Further research revealed that F. prausnitzii metabolizes tacrolimus into less bioactive metabolites, suggesting its abundance could serve as a biomarker for personalized tacrolimus dosing (Guo et al., 2019).

Gut microbiota-derived metabolites also show potential as biomarkers. Compounds such as short-chain fatty acids (SCFAs), branched-chain amino acids (BCAAs), and polyamines are produced by gut bacteria and can influence drug metabolism (Lee et al., 2018). For example, p-cresol, a gut microbial metabolite, competes with acetaminophen for hepatic sulfotransferase SULT1A1, increasing the risk of acetaminophen toxicity (Spanogiannopoulos et al., 2016). Thus, p-cresol concentrations could serve as a biomarker for optimizing acetaminophen dosage and reducing adverse effects.

The integration of probiotics and microbiota-based biomarkers into precision medicine promises to revolutionize therapeutic strategies. Advances in metagenomics, metabolomics, and systems biology will enable the discovery of new probiotic strains and biomarkers that optimize drug efficacy, minimize side effects, and target specific diseases. As research continues to unravel the complex interactions between host, microbiota, and medications, precision medicine will increasingly rely on the dynamic interplay of these factors to deliver personalized treatments.

4.6 Regulation and Application

While the microbiome holds significant therapeutic potential, numerous challenges must be addressed before it can be fully utilized in precision medicine. Delays in the application of microbiome-based therapies may stem from broader difficulties in implementing genomic medicine. For instance, the development of genome-informed therapies often clashes with existing legal and research paradigms (Thompson et al., 2015).

Microbiome-based treatments face additional obstacles due to the diverse nature of therapies, many of which lack parallels in traditional medicine. Physicians often hesitate to integrate genomic findings—and by extension, future microbiome data—into treatments due to uncertainty and insufficient understanding of their significance (Ginsburg et al., 2013). This is evident in the case of Plavix® (clopidogrel), which is frequently prescribed to

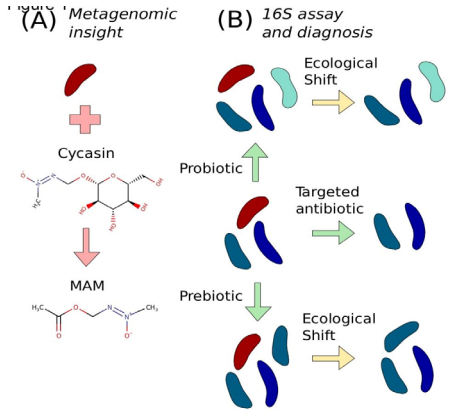

Figure 1. Overview of methods for testing and altering the microbiome in the context of precision medicine. The figure illustrates various complementary approaches that are employed to analyze and modify the microbiome. These methods, outlined in the subsequent text, are critical for advancing the practical implementation of microbiome-based therapies and personalized medicine. The readiness of the microbiome for precision medicine is highlighted, emphasizing the imminent potential for novel therapeutic strategies in this field.

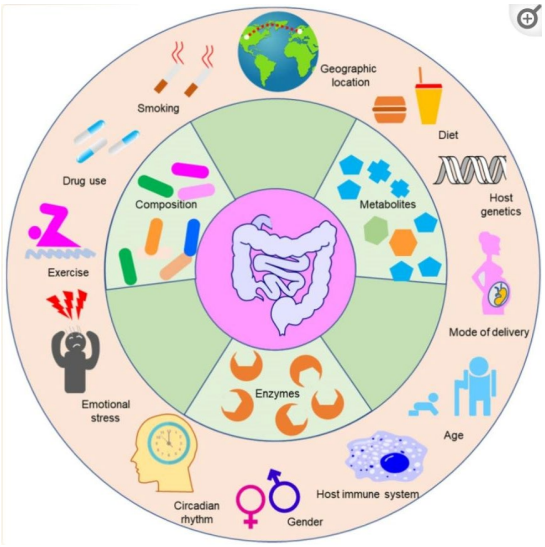

Figure 2. The variables that impact The makeup and capabilities of Gut microbiome

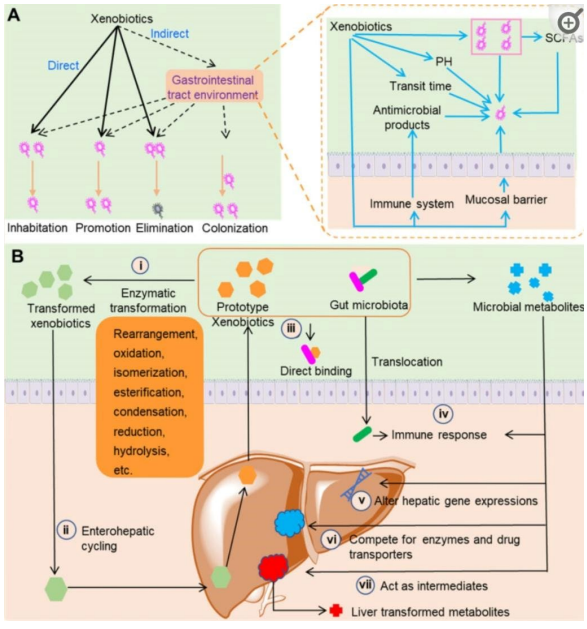

Figure 3. The Interactions between Gut microbiotic and Xenobiotics

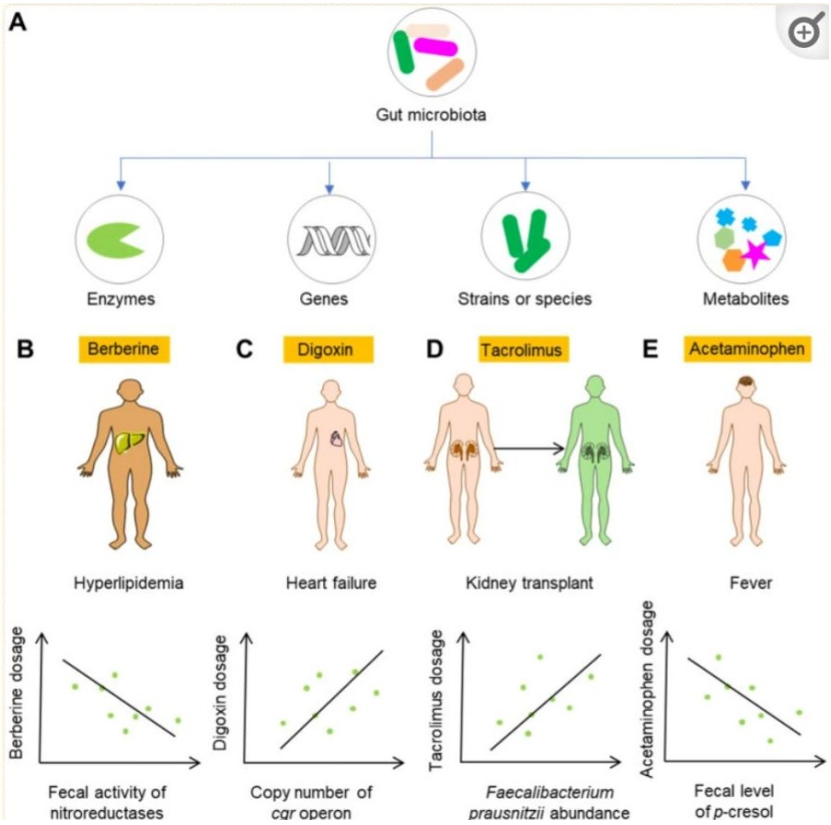

Figure 4. The gut microbiota-based markers for the personalized use of drugs. (A) Possible gut microbiota-based biomarkers for the personalized use of drugs, including genes, enzymes, bacterial strains or species, and gut microbiota metabolites. (B) The fecal activity of nitroreductases is positively correlated with the bioavailability of berberine in treating hyperlipidemia. Thus, the fecal activity of nitroreductases can serve as a biomarker for choosing the dosage of berberine. (C) E. Lenta carrying the cgr operon can inactivate digoxin. Thus, the copy number of cgr operon can serve as a biomarker for choosing the dosage of digoxin or guiding physicians to distinguish patients who are likely to respond favorably to digoxin. (D) F. Prausnitzii can transform tacrolimus into compounds with reduced potency. The abundance of F. Prausnitzii is positively correlated with the need for an increased dosage in patients. (E) Gut microbiota metabolite p-cresol can compete with acetaminophen for liver enzymes, leading to increased toxicity. Thus, fecal p-cresol is a biomarker of a reduced dosage of acetaminophen.

genetically incompatible patients despite an FDA boxed warning about the risks associated with certain CYP2C19 variants (Squibb et al., 2010). Limited insurance coverage and the underutilization of genetic testing contribute to this issue (Johnson et al., 2012).

Fecal microbiota transplantation (FMT) serves as a notable example of the microbiome's therapeutic promise. FMT is highly effective for treating recurrent Clostridium difficile infections, with a success rate exceeding 90% (van Nood et al., 2013). However, the procedure requires practitioners to obtain Institutional Review Board (IRB) approval and informed consent from each patient, which hinders broader adoption. This reluctance stems from the inability to precisely define the active components of donor fecal material, making it challenging to regulate FMT under current FDA standards. Additionally, the long-term implications of large-scale microbiome therapies remain uncertain. While adverse effects of FMT are rare, predicting outcomes across diverse populations is difficult, akin to the unpredictability of gene-environment interactions in genomic medicine (Manuck et al., 2014). Robust statistical power and large sample sizes are essential for meaningful research in this field (Gauderman et al., 2012).

Fortunately, precision microbiome medicine may address some of the challenges faced by genomic medicine. Microbiome research offers a more direct link between environmental factors and biological outcomes, enabling simpler identification of sample populations and greater statistical power. Carefully designed experiments can isolate genetic variation from microbiome and environmental influences. While such studies are more common in controlled animal models (Ellekilde et al., 2014), similar approaches have been applied in human research (Huang et al., 2015). This bottom-up strategy allows genomic research to build on microbiome findings by better accounting for confounding variables.

The microbiome's integration into precision medicine holds promise for conditions influenced by both genetic and environmental factors, such as mental health disorders (Foster et al., 2013). Furthermore, the microbiome provides unique opportunities for studying diseases where genetic variation plays little or no role. For example, dysbiosis—a maladaptive shift in gut microbial communities—drives certain subsets of obesity (Turnbaugh et al., 2016) and inflammatory bowel disease (Frank et al., 2017). These conditions can be investigated in vitro using artificial gut models, offering significant potential for advancing precision therapies (Shah et al., 2016).

Regulatory and logistical challenges remain critical hurdles for the widespread adoption of microbiome precision medicine. The FDA's current stance on probiotics and microbiome therapies highlights the difficulties in regulating and marketing these treatments within traditional frameworks (Morgan et al., 2016; Sun et al., 2016). While this has accelerated product availability, it has also led to concerns about quality control and efficacy (Lewis et al., 2016).

Establishing clear priorities for treatment will be vital to securing support from regulatory bodies, researchers, and clinicians. Avoiding unnecessary testing in low-risk populations or for interventions with limited benefits is essential to advancing microbiome precision medicine efficiently and effectively. By addressing these challenges and capitalizing on the unique advantages of microbiome research, the field can overcome current barriers and unlock its full therapeutic potential.

5. Notable Application: Medically Underserved Communities

Underserved populations, particularly those with low socioeconomic status (SES), represent a promising focus for advancing microbiome-based precision medicine due to the unique advantages it offers. Reduced gut microbiota diversity is closely associated with low SES (Miller et al., 2016). In urban communities, various factors contribute to diminished immunoregulation, including decreased exposure to environmental microbes (Rook et al., 2014), heightened stress (Bailey et al., 2011), and increased prevalence of obesity and dysbiosis (Powell et al., 2016). Additional contributors include reduced physical activity and the proliferation of fast-food establishments, which are linked to health issues such as asthma (Almqvist et al., 2015) and gastrointestinal disorders (Bytzer et al., 2011) mediated by the microbiome.

In contrast to genetic studies, where most identified genomic variants either have large effects but are rare or are common but confer small effects, microbiome research in at-risk populations offers the potential for significant findings due to the presence of biomarkers and substantial effect sizes. These populations provide an informative cohort for advancing microbiome research and understanding its therapeutic implications.

However, extreme caution is needed to avoid misinterpreting associations between microbiome changes (McGuire et al., 2018) or genetic variations (Qureshi et al., 2015) and minority status. Historical shortcomings in cultural sensitivity and access to healthcare services have led to flawed research practices, raising concerns about equity in precision medicine. For example, disparities in access to epidermal growth factor receptor testing reveal that lower income and educational attainment are linked to decreased testing likelihood, independent of health insurance coverage (Lynch et al., 2013; Penson et al., 2011).

To ensure the success of microbiome precision medicine, underserved populations must be active participants in research rather than passive beneficiaries. This approach fosters trust and equity while enabling the development of highly effective therapies tailored to their needs. Addressing the social determinants of health through microbiome precision medicine is not just an opportunity but a necessity. Achieving this goal requires the collaboration of

scientists, physicians, policymakers, and, crucially, the public to promote inclusive research and equitable treatment outcomes.

6. Conclusion

In conclusion, the integration of microbiome research into precision medicine holds transformative potential to enhance patient outcomes by improving diagnostic accuracy, reducing side effects, and enabling personalized treatments for complex conditions. Despite current challenges, such as regulatory barriers and gaps in understanding microbiome-host interactions, a coordinated effort among scientists, clinicians, policymakers, patients, and communities is essential. Advancing our knowledge of the microbiome's role in human health and its environmental interactions will pave the way for its incorporation into mainstream clinical practice. With continued collaboration, microbiome-based precision medicine can revolutionize healthcare and address unmet medical needs on a global scale.

Author contributions

A.N.P. conceptualized the study, designed the methodology, and drafted the manuscript. W.M. contributed to data analysis, interpretation of results, and critical review of the manuscript. Both authors approved the final version of the manuscript.

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Competing financial interests

The authors have no conflict of interest.

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