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Gut Microbiota in Drug Metabolism: A New Frontier in Precision Medicine

Harmanjot Kaur*, Amanpreet Kaur, Monika Singh

Faculty of Pharmaceutical Sciences, PCTE Group of Institutes, Ludhiana, Punjab 142021
hansraharman3@gmail.com talwaraman1234@gmail.com monikasingh14000@gmail.com

Abstract:

The gut microbiota, an intricate network of trillions of microbes, is responsible for drug metabolism and affects pharmacokinetics, efficacy, and toxicity. Recent findings in pharmacology and microbiome research emphasize the importance of gut microbes in modulating drug absorption, biotransformation, and excretion, making them a key driver of interindividual variability in drug response. Microbial enzymes activate, inactivate, or modify drug structures and affect therapeutic responses. Dysbiosis, a disruption of gut microbial composition, has been implicated in disrupted drug metabolism leading to adverse drug reactions and failure of therapy. As precision medicine takes centre stage, knowledge of the role of gut microbiota in drug metabolism opens the door for microbiome-based therapies, including probiotics, prebiotics, and faecal microbiota transplantation, to tailor drug therapy. Pharmacometagenomics is a new field that seeks to incorporate microbiome profiling into customized drug regimens, minimizing drug response variability and enhancing patient outcome. This review delves into the complex relationship between gut microbiota and drug metabolism, addresses important microbial enzymes for drug biotransformation, and identifies potential strategies to capitalize on microbiome data for precision pharmacotherapy. Through connecting microbiology with pharmacology, research into the gut microbiota provides new understandings into tailored treatment strategies and influencing the course of drug discovery and clinical applications.

Keywords: Gut microbiota, Drug metabolism, Pharmacokinetics, Precision medicine, Pharmacometagenomics, Microbial enzymes Microbiome-based therapies

1. Introduction:

The human gut harbours a rich and complex community of microorganisms, which together form the gut microbiota. The microorganisms, such as bacteria, viruses, fungi, and archaea, are essential for overall health. The gut microbiota is not just a passive inhabitant of the gastrointestinal tract but an active player in several physiological processes, affecting digestion, immunity, metabolism, and even neurological processes [1]. Scientific research conducted over the last few decades has identified that the microbial community in this area plays a vital role in the development of homeostasis and warding off diseases [2].

Individual variability in gut microbiota exists based on factors such as diet, genetics, lifestyle, the intake of drugs, and exposure to the environment [3]. The phyla of the human gut, consisting of dominant bacterial phyla, are Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria. These microbes aid digestive health by decomposing complex carbohydrates, proteins, and fats to yield short-chain fatty acids, which are utilized as energy substrates for cells in the colon and also function to control metabolic processes [4]. They also synthesize key vitamins like vitamin K and B-complex vitamins, aiding different physiological functions [5]. The gut microbiota is essential for immune system modulation in addition to digesting. By teaching the immune system to distinguish between dangerous pathogens and helpful microbes, it helps avoid needless immunological reactions that might result in autoimmune disorders. In order to preserve a healthy gut environment, beneficial bacteria generate antimicrobial compounds that prevent the formation of dangerous infections [1][4]. Dysbiosis, or disturbances in this delicate equilibrium, has been connected to a number of

illnesses, such as diabetes, obesity, inflammatory bowel disease, and even mental health issues. The gut-brain axis—the relationship between gut bacteria and brain function—has also been the focus of recent studies [6][7]. Gut bacteria create neurotransmitters and microbial metabolites that affect behaviour, mood, and cognitive processes. Maintaining a healthy microbiome is crucial since imbalances in the makeup of the gut microbiota have been linked to disorders including anxiety, depression, and neurodegenerative illnesses [5].

The function of the gut microbiota in drug metabolism has been a central area of focus for precision medicine. Some gut microbes can activate, inactivate, or metabolize drugs, modulating their activity and toxicity. Elucidating these microbial-pharmaceutical interactions holds the promise to transform personalized medicine, making it possible to design treatments for an individual patient based on their microbiome signature [7]. As studies continue to reveal the complex interaction between gut microbiota and human health, it is increasingly clear that having a balanced microbiome is critical to overall well-being. A balanced diet, probiotics, prebiotics, and lifestyle changes can all contribute to a diverse and stable gut microbiota. As microbiome science continues to advance, the potential of gut microbes could unlock novel therapeutic strategies for numerous diseases, eventually redefining the future of healthcare [3].

2. Gut Microbiota and Drug Metabolism:

Drug metabolism is significantly influenced by the gut bacteria through a number of enzymatic mechanisms. These microbial enzymes have the power to change the toxicity, bioavailability, and effectiveness of medicinal molecules [8]. Gut microorganisms primarily carry out the following enzymatic processes: reduction, hydrolysis, deconjugation, and demethylation. Microbial enzymes frequently break down certain chemical bonds to convert medications into active or inactive metabolites, in contrast to hepatic enzymes, which mostly oxidize and conjugate pharmaceuticals for excretion [6][8]. Bacterial nitro reductases catalyse the reduction of azo compounds and nitro-containing medications, which is one of the most well-known microbial enzymatic activities. In order to activate prodrugs like sulfasalazine, which is used to treat inflammatory bowel disease, this is necessary [11].

Drug deconjugation is further facilitated by microbial β-glucuronidases and sulfatases, which reactivate pharmaceuticals expelled in bile and affect their enterohepatic circulation. Drugs like irinotecan, a chemotherapeutic medication whose toxicity is increased by bacterial β-glucuronidases, may be affected by this [9]. Hydrolases are another type of microbial enzyme that affects drug metabolism and absorption by hydrolyzing glycosides, amides, and esters. Similar to hepatic cytochrome P450 enzymes, many bacteria also carry CYP-like enzymes that have the ability to alter medications in novel ways [7][8]. For example, it has been suggested that bacterial demethylases and dehydrogenases change cardiac glycosides like digoxin, changing its pharmacological properties. These microbial changes highlight how crucial the gut microbiota is in predicting medication response, which makes it a crucial component of precision medicine [9].

3. Hepatic and Microbial Drug Metabolism Comparison

The two main processes that control drug metabolism are the microbial metabolism that takes place in the gut and the hepatic (liver) metabolism. Despite the fact that both systems are essential to drug biotransformation, their processes, enzyme specificity, and effects on therapeutic effectiveness are very different [10][2]. Traditionally, hepatic drug metabolism is separated into Phase I and Phase II processes, which are mostly mediated by sulfotransferases (SULTs), UDP-glucuronosyltransferases (UGTs), and cytochrome P450 (CYP) enzymes. Hepatic CYP enzymes oxidize medications during Phase I, adding functional groups that improve their solubility. Conjugation processes in Phase II add compounds like glutathione, glucuronic acid, or sulphate, which increases the drug's water solubility and facilitates its excretion through bile or urine. Usually, the goal of these procedures is to detoxify and remove narcotics from the body [11][13].

In contrast, reductive, hydrolytic, and deconjugation reactions are the main processes involved in microbial drug metabolism. Gut microbial enzymes frequently reactivate medications by degrading their conjugates, in contrast to hepatic enzymes. This may result in changed therapeutic results, higher toxicity, or longer medication activity. For instance, the gut's bacterial β-glucuronidases have the ability to reverse hepatic glucuronidation, which results in increased toxicity and

drug reabsorption [13]. Microbial metabolism is also extremely individual-specific, impacted by gut microbiota makeup, antibiotic usage, and nutrition [9]. Microbial metabolism can either activate, inactivate, or alter medication effects in an unpredictable way, whereas hepatic metabolism usually decreases drug activity and improves clearance [7].

The interaction between the gut and liver microbiota emphasizes the need for a more comprehensive personalized medicine strategy, where medication therapy might be optimized by using individual microbiome profiles. In precision medicine, knowing these interactions helps reduce side effects, increase therapeutic efficacy, and anticipate medication response variability [12].

4. Gut Microbiota and Prodrugs: Implications for Drug Activation

Pharmacologically inert substances known as prodrugs must undergo biotransformation into active metabolites in order to have therapeutic effects. Although prodrug activation is mostly mediated by hepatic enzymes, namely cytochrome P450 (CYP) enzymes, gut microbiota has become an important factor in drug metabolism. Through enzymatic processes, the gut microbiota influences the activation, modification, or inactivation of different prodrugs, affecting the drug's effectiveness, bioavailability, and patient response. Optimizing medication therapy requires an understanding of these microbial contributions, especially in the age of precision medicine [11][13].

To activate prodrugs, gut microorganisms use a range of enzymatic mechanisms. Among the most important changes that gut bacteria mediate are reduction, hydrolysis, and deconjugation. For instance, sulfasalazine, a medication used to treat inflammatory bowel disease, is activated by azoreductases present in certain gut flora [12]. Sulfapyridine and 5-aminosalicylic acid (5-ASA), the prodrug sulfasalazine's potent anti-inflammatory components, are released when colonic bacteria break its azo link, rendering it inert. For the medication to have a therapeutic impact in the gut, this microbial activation is necessary [10][14]. Bacterial β-glucuronidases, which affect drug activation and recycling, are another example. These enzymes aid in the reabsorption and sustained action of glucuronide-conjugated medications by hydrolyzing them after they have been eliminated into the stomach through bile [6]. The effectiveness of the anticancer prodrug irinotecan is influenced by this mechanism. However, acute toxicity, as diarrhoea caused by irinotecan, can result from high bacterial β-glucuronidase activity, demonstrating the dual involvement of microbial metabolism in both drug activation and side effects [15].

Additionally, prodrugs that include nitrate, including nitrofurantoin and other cardiovascular medications, are activated by gut microbes. These chemicals are reduced by bacterial nitroreductases, which increases their therapeutic effect [13]. Digoxin is one example of a cardiac glycoside that can be metabolized by gut bacteria, which can impact patient response and therapeutic efficacy. Digoxin's effectiveness in certain people may be diminished by the inactivation of certain gut bacteria, such as Eggerthella lenta, according to studies [16].

Table 1: Gut microbiota and Prodrug activation

Prodrug	**Active Metabolite**	**Microbial Enzyme Involved**	**Microbial Species**	**Therapeutic Use**	**Effect of Microbiota on Drug Activation**
Sulfasalazine	5-Aminosalicylic Acid (5-ASA) & Sulfapyridine	Azoreductase	*Clostridium*, *Bacteroides*	Inflammatory Bowel Disease (IBD), Rheumatoid Arthritis	Gut bacteria cleave the azo bond, activating the drug locally in the colon.

Irinotecan	SN-38	β-Glucuronidase	*Clostridium*, *Escherichia coli*	Chemotherapy (Colon Cancer)	Microbial β-glucuronidase reactivates SN-38, increasing toxicity and side effects like diarrhea.
Digoxin	Inactive Metabolites	Cardiac Glycoside Reductase	*Eggerthella lenta*	Heart Failure, Arrhythmias	Some gut bacteria inactivate digoxin, reducing its therapeutic effect.
Clopidogrel	Active Thiol Metabolite	Unknown Microbial Enzymes	*Bacteroides*, *Prevotella*	Antiplatelet Therapy	Gut microbiota modulates the drug's activation, influencing its antiplatelet effects.
Prontosil	Sulfanilamide	Azoreductase	*Clostridium*, *Bacteroides*	Antibacterial (Sulfa Drug)	Gut bacteria activate prontosil by cleaving the azo bond, releasing sulfanilamide.

5. Microbiome-Based Therapeutic Strategies for Precision Medicine

The human gut microbiota is a prime target for precision medicine as it is essential for immunological control, medication metabolism, and the advancement of illness. Researchers are creating microbiome-based therapeutic approaches to maximize medication efficacy, reduce side effects, and customize medical treatments as scientific knowledge of the microbiome grows. These tactics, which attempt to alter the makeup of gut microbes for better health outcomes, include probiotics, prebiotics, fecal microbiota transplantation (FMT), microbiome-targeted medications, and synthetic biology techniques [12][17]. Probiotics, which are live beneficial bacteria that aid in reestablishing microbial balance, are among the most widely used microbiome-based therapies. It has been demonstrated that probiotics, such as Lactobacillus and Bifidobacterium species, increase immunological function, decrease adverse effects linked to antibiotics, and improve medication metabolism [15]. Probiotic supplements, for instance, can improve medication tolerance and lessen gastrointestinal toxicity by addressing gut dysbiosis brought on by chemotherapy or antibiotics. Certain probiotics have also been researched for their ability to alter medication response, which might increase the efficacy of immune checkpoint inhibitors in cancer treatment, for example [18].

Another potential tactic is the use of prebiotics, which are indigestible food fibers that encourage the development of good gut flora. Prebiotics have the ability to affect immunological responses and medication metabolism by specifically increasing the activity of microorganisms that promote health [16]. Fructooligosaccharides (FOS) and inulin, for example, might increase the synthesis of short-chain fatty acids (SCFAs), which have metabolic and anti-inflammatory properties. These substances are useful adjuncts in precision medicine because they can help control diseases including inflammatory bowel disease, diabetes, and metabolic syndrome [19].

In order to reestablish a normal gut microbiome, a more sophisticated method is fecal microbiota transplantation (FMT), in which feces from a healthy donor is transferred into a patient. FMT has shown great promise in treating gut dysbiosis-related Clostridium difficile infections. FMT is being investigated for its potential to treat neurological problems including Parkinson's disease, autoimmune diseases, and metabolic disorders in addition to infection management. FMT is a potent tool in precision medicine because it can restore microbial imbalances by transferring a healthy microbiome [20]

Another creative tactic is the creation of medications that target the microbiota. In order to improve treatment results, these medications are made to specifically alter gut microbial activity. For instance, by lowering dangerous drug reactivation in the gut, inhibitors of bacterial β-glucuronidase enzymes are being researched to stop irinotecan-induced toxicity in cancer patients [16]. Similarly, the ability of metabolites generated from the microbiome, such SCFAs and secondary bile acids, to influence inflammation and immunological responses is being investigated [19].

New opportunities for modifying gut microorganisms to carry out certain therapeutic tasks are presented by developments in synthetic biology. Researchers are creating genetically altered probiotics that may break down pollutants, produce medicinal substances, or control immune responses in the gut. For instance, the potential of modified Escherichia coli Nissle 1917 to generate anti-inflammatory compounds for the treatment of inflammatory bowel illness has been investigated. Precision medicine and focused medication distribution may be transformed by these bioengineered microorganisms [20][21].

More accurate illness diagnosis and therapy may be possible if microbiome research advances and microbiome analysis is incorporated into clinical practice. Clinicians may be able to customize therapies based on a patient's gut microbial makeup by employing metagenomics and metabolomics to profile their personalized microbiome and predict individual medication responses. This strategy may lessen adverse medication reactions and enhance treatment results for ailments ranging from mental illnesses to cancer [22].

Table 2: Microbiome-Based Therapeutic Strategies for Precision Medicine

Strategy	Description	Application
Probiotics	Live beneficial bacteria that support gut health.	Improve drug tolerance, aid digestion, and enhance immunity.
Prebiotics	Non-digestible fibres that promote the growth of good bacteria.	Modulate gut microbiota to support metabolic and immune functions.
Faecal Microbiota Transplant (FMT)	Transfer of healthy donor gut bacteria to restore balance.	Used for Clostridium difficile infection, research in autoimmune and neurological diseases.

Microbiome-Targeted Drugs	Small molecules that selectively modulate gut microbes.	Treats metabolic disorders, inflammatory diseases, and infections.
Metagenomics & Metabolomics	Analyzing gut microbiota composition and functions for precision therapy.	Personalized drug dosing, predicting treatment response.

6. Advances in Microbiome Analysis and Its Role in Pharmacokinetics

Pharmacokinetics—the absorption, distribution, metabolism, and excretion (ADME) of drugs—is influenced by the gut microbiota, which is a key factor in drug metabolism. Researchers are learning more about how gut bacteria impact medicine toxicity and efficacy thanks to recent developments in microbiome analysis. Personalized medicine techniques that improve medication therapy based on an individual's microbiome profile are being made possible by technologies like metagenomics, metabolomics, and bioinformatics, which are transforming the study of host-microbiome interaction [23].

Metagenomic sequencing, which enables the thorough characterization of microbial communities within the gut, is one of the most important developments in microbiome study. The identification of bacterial species and their functional genes involved in drug metabolism is made possible by high-throughput sequencing methods including whole-genome shotgun sequencing and 16S rRNA sequencing. These techniques have shown that some gut microorganisms' express enzymes that can change the pharmacokinetics of medicines by activating, deactivating, or altering them. Bacterial β-glucuronidases, for instance, have the ability to reactivate medications that are eliminated by hepatic glucuronidation, which might affect drug toxicity and clearance [24][25].

Another effective approach that sheds light on the biochemical byproducts of microbial metabolism is metabolomics. Researchers can ascertain how gut bacteria affect medicine bioavailability by examining metabolites generated by microorganisms using methods such as nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry (MS). For example, short-chain fatty acids (SCFAs) generated by the microbiota can alter gut pH, which can impact medication absorption and solubility [19][26]. Furthermore, metabolomic profiling has been used to investigate the microbial metabolism of digoxin, sulfasalazine, and irinotecan, emphasizing the part gut bacteria play in medication biotransformation [27]. When it comes to combining pharmacokinetic models with microbiome data, bioinformatics and machine learning are essential. To forecast drug-microbiome interactions, computational techniques examine extensive metabolomics and microbiome sequencing data. Personalized medication dosage methods can be developed by using machine learning algorithms to detect microbial fingerprints linked to drug metabolism. By taking into account a person's microbiome composition, these prediction models may reduce negative medication responses and enhance therapeutic efficacy [23].

The influence of the microbiota on enzymes and drug transporters has also been the subject of recent research. In order to affect medication absorption and distribution, gut bacteria can alter the expression of transport proteins like P-glycoprotein (P-gp) and host drug-metabolizing enzymes like cytochrome P450 (CYP) enzymes. Microbial metabolites, for instance, have the ability to either stimulate or inhibit hepatic CYP enzymes, which might impact how medications like antidepressants, statins, and warfarin are metabolized [25][27]. Reducing interindividual variability in medication response and improving drug dosage techniques are two benefits of understanding these interactions [22]. Precision medicine that is guided by microbiome analysis is being made possible by the incorporation of microbiome data into pharmacokinetics. Clinicians may be able to anticipate drug efficacy and adjust treatment plans by analyzing a patient's

gut flora before writing a prescription. This strategy is especially pertinent to diseases like cancer treatment, antibiotics, and immunosuppressants where the gut microbiota has a major impact on medication response [28].

7. Challenges and Ethical Considerations in Microbiome Research

With the growing body of microbiome research and its increasingly understood roles in drug metabolism, disease treatment, and personalized medicine, a number of challenges and ethical concerns need to be met. While there is promise in microbiome-directed pharmacotherapy, issues surrounding study replicability, interpersonal variability, data privacy, regulatory control, and equitable access pose ongoing challenges. Solving these problems is necessary to ensure that microbiome-based treatments are both scientifically valid and ethically applied [29][30]. Interindividual variability is one of the main problems in microbiome research. Individual differences in gut microbiota composition can be attributed to a variety of variables, including antibiotic usage, environment, nutrition, and genetics. The development of standardized microbiome-based therapeutics is made more difficult by this diversity since a therapy that works for one individual may not work for another or even be detrimental. Predicting long-term drug-microbiome interactions is also difficult because of the dynamic nature of the microbiome, which can alter over time as a result of outside factors [31].

The uniformity and reproducibility of microbiome research are important additional concerns. Research studies may yield conflicting results due to variations in sample collecting procedures, sequencing methodologies, and study design. It is challenging to evaluate results and create precise clinical guidelines for microbiome investigation due to the absence of well recognized methodologies. Translating research findings into clinical practice requires standardizing microbiome research methodology and creating reliable bioinformatics tools to interpret microbiome data [30][31]. As microbiome sequencing becomes increasingly common, ethical questions about data security and privacy are becoming more pressing. Data from a person's human microbiome can provide information about their history, health, and even their risk of contracting diseases. Microbiome profiles have the potential to be utilized for identification due to their uniqueness, which raises issues regarding genetic discrimination or illicit data usage. Protecting people's microbiome information will need appropriate data anonymization, encryption, and moral data-sharing procedures. Prior to the widespread use of microbiome-based therapies, regulatory and legal issues must also be resolved. Different regulatory categories now govern microbiome-based goods, including probiotics, fecal microbiota transplantation (FMT), and medications that target the microbiome. This results in inconsistent approval and supervision processes. To avoid uncontrolled usage and possible patient harm, it is essential to establish precise regulatory frameworks for microbiome-based therapies, guarantee thorough safety and effectiveness testing, and establish standards for clinical implementation [17][29][30].

Another ethical issue is fair access to microbiome-based treatments. Personalized medicine strategies, such as microbiome-directed therapies, can be costly and out of reach for some populations, perpetuating healthcare inequalities. Ensuring that microbiome research is for the benefit of diverse populations and does not increase the gap in healthcare accessibility is a critical ethical issue. Microbiome studies in various ethnic and socioeconomic groups are essential to avoid biases in microbiome-based therapies.[31]. Finally, patient autonomy and informed consent in microbiome research are paramount ethical concerns. Because microbiome analysis may disclose sensitive health data, participants should be thoroughly informed of how their data will be utilized and any risks involved. Open communication among researchers, healthcare professionals, and patients is needed to establish trust and guarantee ethical involvement in microbiome research [32].

8. Future Directions in Gut Microbiota and Precision Medicine

The gut microbiota is becoming a major contributor to the development of precision medicine due to our increasing understanding of its involvement in both health and illness. Future research will concentrate on using the complex relationships between gut bacteria and the human body to create individualized treatment plans, enhance medication therapy, and enhance illness prevention. The next wave of microbiome-based precision medicine will be driven by advancements in microbiome engineering, targeted medicines, microbiome profiling, and analytics powered by artificial intelligence [33]. Precision therapies using tailored microbiome profiling is one of the most exciting new avenues. A

detailed analysis of a person's gut microbiota is now feasible because to developments in metagenomics, metabolomics, and transcriptomics [34][35]. Clinicians will be able to more precisely anticipate medication response and adjust therapies by combining microbiome data with genetic and metabolic data. Microbiome-informed dosage regimens for antibiotics, chemotherapy, and immunosuppressants, for instance, may improve therapeutic effectiveness and decrease adverse drug responses [34].

Another crucial area of future study is the creation of biomarkers based on the microbiome for the diagnosis of diseases and the response to therapy. Certain microbial signatures have previously been linked to illnesses such neurological disorders, metabolic disorders, and cancer. Clinicians will be able to employ non-invasive microbiome testing for prognosis, therapy monitoring, and early illness identification after these indicators have been found and validated. This has the potential to transform the treatment of conditions including diabetes, inflammatory bowel disease (IBD), and even mental health conditions like depression [36][37]. Microbiome-directed therapeutics, such as probiotics, prebiotics, postbiotics, and microbiome-modulating pharmaceuticals, will contribute importantly to precision medicine. New-generation probiotics designed to target therapeutic molecules, modulate immune function, or increase drug metabolism are in active development [34]. Precision prebiotics that can selectively feed good microbes may restore balance of gut microbes in dysbiotic patients. New microbiome-derived pharmaceuticals, e.g., small-molecule inhibitors of pathogenic microbial enzymes, can also be developed as novel treatment modalities for microbiome diseases [19][37].

The application of microbiome science to clinical practice and public health, in addition to therapeutic developments, will be a major area of emphasis. In order to provide individualized nutritional advice, lifestyle changes, and microbiome-targeted treatments, future healthcare systems may integrate routine microbiome screening into patient care. To promote international research cooperation and advance our knowledge of the connections between microbiome and illness, extensive microbiome databases and biobanks will be created [38][39].

9. Conclusion:

Drug effectiveness, toxicity, and interindividual heterogeneity in treatment responses are all influenced by the gut microbiota, which has become a crucial factor in drug metabolism. Research on the microbiome is transforming our knowledge of pharmacokinetics and pharmacodynamics as a new area in precision medicine, opening the door to more individualized treatment plans. Researchers may now understand the intricate relationships between gut microorganisms and medications by utilizing developments in metagenomics, metabolomics, and bioinformatics. This allows for the creation of medication treatments that are guided by the microbiome. Predicting patient-specific treatment responses and improving drug dosage are two of the most exciting uses of gut microbiota research. Precision dosage techniques that reduce side effects while optimizing therapeutic benefits are made possible by an understanding of how microbial enzymes activate, inactivate, or alter medications. Furthermore, the identification of biomarkers based on microbiomes has the potential to advance customized therapy by predicting diseases and tracking their effectiveness.

Even with these developments, a number of issues still need to be resolved, such as the diversity of microbiome composition, the repeatability of microbiome research, and moral issues pertaining to data privacy and fair access to treatments based on microbiomes. Microbiologists, pharmacologists, data scientists, and clinicians must work with collaboratively to address these issues in order to create standardized procedures, reliable computational models, and regulatory frameworks for treatments based on the microbiome.

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