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When Cultures Meet: The Landscape of "Social" Interactions between the Host and Its Indigenous Microbes

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Animals exist as biodiverse composite organisms that include microbial residents, eukaryotic cells, and organs that collectively form a human being. Through an interdependent relationship and an inherent ability to transmit and reciprocate stimuli in a bidirectional way, a human body or the holobiont secures growth, health, and reproduction. As such, the survival of a holobiont is dependent on the maintenance of biological order including metabolic homeostasis by tight regulation of the communication between its eukaryotic and prokaryotic residents. In this review an overview and perspective are provided on the bidirectional communication between microbes and their host in mutually nurturing biochemical, biological, and social interconnected relationships between the components of the holobiont. An emphasis is placed on exemplifying microbiome-mediated effects on host functions—aiming to integrate microbiome functionality to host physiology, be it health or disease. Nutrition, immunology, and sexual dimorphism have been traversed extensively to reflect on health and mind states, social interactions, and urbanization defects/effects. Finally, examples of molecular mechanisms potentially orchestrating these complex transkingdom interactions are provided.

1. Introduction

Humans harbor trillions of microbes, six orders of magnitude smaller in size than us, that in concert support essential host functions in an inextricable manner (e.g., critically drive aspects of digestion, metabolism, behavior, and immune functions). These complex interactions between the host and its prokaryotic residents in the human body are only beginning to be unraveled. Currently, we describe the microbe–host interactions as a form of symbiosis, in which each contributing partner, of these constant interactions, net gains from its collective advantages. As such, the host genome, cells, and organs in concert with all their microorganisms represent nonseparable components that together make up a metaorganism constituting a unique and interconnected functional unit, with defined boundaries, i.e., an individual. Such an individualized metaorganism is structured by a distinct eukaryotic–-prokaryotic combination that is profoundly variable and dynamic and evolves while integrating changes in diet, physical activity, perception, and desire in order to facilitate the development and maturation of a human being along its lifespan.

2. We Nurture an Intricate Relationship with Our Symbiotic Microbes

Humans and their indigenous microbiomes are uniquely symbiotic in a number of facets. Indeed, many human genes are homologous to bacterial genes that are predominant in

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metabolism and communication, suggesting areas of overlapping functions.[1] The word "commensal microbes" arises from the Greek word "cum mensa," eating together, and illustrates the convoluted relationship between the mammalian host and its residential microbes. We indeed "eat together"—gut microbes assist us in the digestion of the food we eat, sloughed off cells of our intestine, and provide us with functional metabolites and vitamins that would otherwise have been literally "lost in translation." We reciprocate by supplying microbes with nutrients and shelter their existence in our body. Acting as guardians of self, our microbes also generate a first-line shelter against unwanted pathogenic invaders by releasing antimicrobial molecules or transmitting signals to activate the immune system. Germ-free (GF) mice, devoid of exposure to living microbes, represent an artificial man-made system enabling us to assess the impact of lack of microbiomes on mammalian physiology and to in vivo model and monitor microbe–host interactions. As an organism, a GF mouse is largely impaired in all organ functions, including the intestines, liver, muscle, brain, and multiple arms of the immune system. However, repopulating GF mice with microbes generally restores organ function including the host immune system.[2–5] Gut–microbe immune interactions are bidirectional, enable the development of an immune system unique to each individual, and have the ability to protect its host from pathogenic infections or from autoimmune reactions. The host, with its unique individual genetic makeup, reciprocates by eliciting signals guiding diversification and richness of microbes in a closely regulated spatial and temporal manner.[6] Interestingly, recent data suggest that genes related to diet, metabolism, and immunity appear to dominate in efficacy to shape gut–microbe expansion and diversification in a newly formed offspring.[7] However, the full scope of this intricate and powerful mechanistic relationship between host genetics and microbiome composition is yet to be determined.

Our indigenous microbes support us in a variety of ways by releasing molecules that often, but not always, exert synergistic effects on body functions. These are even suggested to span optimal brain development and subsequent functioning.[8,9] For example, recent theories suggest that in the absence of microbes, humans would not have developed the current level of cognitive performance.[10] While this claim may remain speculative, emerging evidence suggests that microbes constitute a potential regulatory facet impacting brain function and putatively even behavior impacting the human trait of sociability. For example, GF mice raised in the absence of microbes show drastic alterations in sociability, anxiety, and increased stress sensitivity, as judged by behavioral paradigms and increased levels of cortisol.[11,12] The true scope and mechanisms of such putative gut–brain interactions merit further studies and experimental validation in humans.

3. Culture Meets Culture: Can Microbes Teach Us Sociology?

One can draw parallels between the coordinated activity of the host and its endogenous microbial ecosystems to that achieved by collective cooperation between individuals in a society. In order to ensure optimal organ function in a human being, communication and interactions between its "human" and "microbial" components are necessary (**Figure 1**). By comparison, human beings must interact with other human beings through social interactions in order to achieve a goal (i.e., cooperates, social movement groups, etc.). Certain collectively beneficial goals require the contributions of a variety of functions from many individuals—a result that cannot be achieved by a single individual. Hence, individuals complement each other in skills to achieve crucial societal goals; other functions are fully achieved by one type of individual, but are meaningless without the functions performed by others. Similarly, GF mice in which the holobiont microbial component is missing are compromised in many traits related to their interactions with the outside world (i.e., malfunctioned immune system, metabolism, etc.). Likewise, human individuals and their interactions are not only beneficial for the group as a whole but the collective and social interactions among the group reward its members on emotional, functional, and social levels.

In contrast, opposing "interests" within members of a human society may lead to contexts favoring competition, dispute, and even war. These can be paralleled within the holobiont when the host and its microbes fail to properly communicate, thereby leading to dysbiosis and disease risk. In these conflicted situations one of the partners exploits the resources of the other, while at the extreme, such long-standing alterations become permanent and result in disease

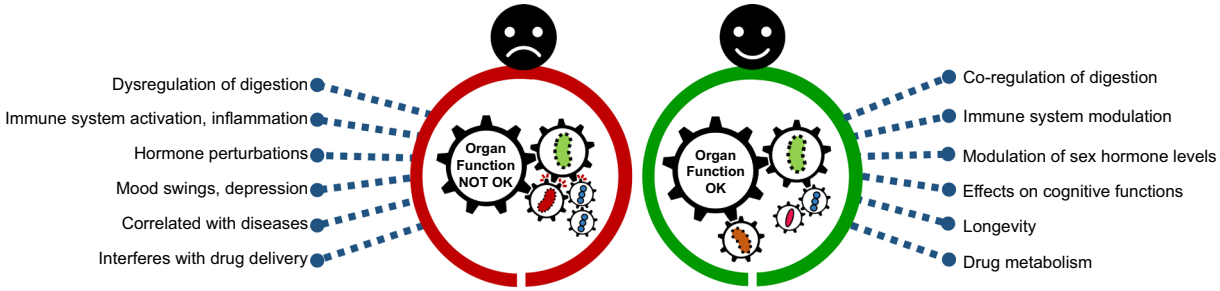

Figure 1. Gut–microbiome interactions influence the physiology of the host. The healthy individual (green) is shown to have cooperative, symbiotic interactions with its microbiome. In this state, both bacterial species and the host are benefited, as shown by an operational clockwork mechanism. The benefits to the host are listed to its right. The malfunctioned individual (red) is shown to have dysbiotic interactions with its microbiome. In this state, both bacterial species and the host suffer, as shown by a faulty clockwork mechanism. The host's ailments are shown to the left.

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pathogenesis. Host genetic susceptibility is a major prerequisite for such alterations[13–15] (Figure 1).

4. Why May We Benefit from Harboring Large Microbial Communities inside Us?

4.1. Commensal-Mediated Maintenance of Sex Hormones

An example of a cooperative host–microbiome function is the production and maintenance of normal system sex hormone levels and balance. Sex hormone levels are intimately connected to the social functions of human beings and were recently found to be modulated by a concerted activity of the host and its microbiome. For example, both estrogen and testosterone have been shown to influence microbial communities by increasing diversification of the gut microbiome.[16,17] Gut microbes, in turn, tune metabolism and systemic levels of these hormones through secretion of β-glucuronidase, an enzyme that deconjugates estrogens into their active forms. When this process is impaired by a dysbiotic microbiome, characterized by lower microbial diversity, the decrease in deconjugation results in a reduction of circulating estrogens. This, in turn, affects many vital aspects of body functions including cognitive functions, intestinal mucin production, and reproduction ability. Reduced levels of circulating estrogens are associated with the development of conditions such as obesity, metabolic syndrome, and immune function.[18–20] The implications of host hormone to gut–microbe interactions are still in their infancy and research addressing the considerable changes in hormonal activity during puberty, adolescence, and menopause are highly warranted as these hormone transition periods are often associated with mental health problems.[21]

On a functional level, a recent study suggests that early-life microbial exposure may determine sex hormone levels and modify progression to autoimmunity in the nonobese diabetic (NOD) mouse model of type 1 diabetes (T1D).[17] In this study, commensal microbes elevated serum testosterone and protected NOD males from T1D. Furthermore, transfer of gut microbes from adult males to immature females altered the recipient's microbiota, elevated testosterone levels, caused metabolic changes, and, importantly, led to a robust T1D protection.[17]

4.2. Gut Microbes Are Essential for Food Digestion

Gut microbes are pivotal for the host's digestion. Indeed, a mammalian host is unable to complete digestion of the entirety of food or to de novo produce all food-related vitamins that are critically important for a healthy living. Sharing the digestive capability with its "microbial self" ensures a supply of essential vitamins and nutrients upon food digestion. An extreme example of this mutualistic behavior occurs immediately after birth, when the mother begins to generate breastmilk for the newborn, and this nutritional fluid, loaded with lipids, also contains oligosaccharides (human milk oligosaccharides) that are digested only with the aid of a certain bacteria from the *Bifidobacterium* genus. These commensals represent bacteria that act as symbionts to the host and nutritionally support by releasing molecules that have anti-inflammatory immune modulation functions.[5,22–24] Likewise, in adults, Firmicutes and Bacteroidetes are prominent in the gut, and metabolize dietary plant polysaccharides, which are otherwise indigestible by the mammalian host.[25,26]

4.3. Gut Microbes Assist in Holobiont Metabolism by Acting as a "Bioreactor" System

The human body can also be viewed as a bioreactor, composed of human organs and also the microbial residents. This highly dynamic bioreactor is in constant operation in digesting diet, thereby ensuring proper energetic input to secure its functions. While each partner contributes to the reactor activity, there are specific processes unique to each partner. The host has a powerful machinery to control food intake, while the gut microbes perform multiple vital and unique biosynthetic features.[27] These include essential vitamin and amino acid production,[28–31] modulation of host-derived molecules, conversion of host-generated primary bile acids into bioactive secondary bile acids,[32] and degradation of food-derived molecules into ones digestible by the host.

An example of such microbiome-tuned bioreactor activity is the microbial regulation of tryptophan metabolism. The current view holds that only 10% of the microbes within a human being possess the ability to metabolize tryptophan,[33] leaving 90% of the microbiome community unable to generate tryptophan metabolites that are intimately linked to immunity, metabolism, circadian rhythm, and behavior. This finding suggests that microbe-regulated tryptophan metabolism is highly variable from individual to individual, depending on his/her unique signature of tryptophan-producer and -nonproducer strains. This variability may generate personal traits of health and disease susceptibility since tryptophan metabolites are known to influence many vital body functions including metabolism and immunity.[29,30] Another example is the capacity of gut microbes to execute xenobiotic metabolism of drugs.[34] Recent data from the cancer biology field imply that future choice of individual anticancer drugs may require a metagenomic screen based on the gut–microbiome profile.[35] Likewise, levels of metphormin,[36] antipsychotics,[37,38] and digoxin have been shown to individually vary based on microbiome diversity.[39–41] Notably, these rather generic and general microbiome functions have been found to be performed by microbial molecular mechanisms, which often implicate individual "driver" strains or microbial signatures of limited complexity, conferring crucial bioactive signals to the eukaryotic host.

4.4. Gut Microbes Shape and Complement the Holobiont Immune Function

The great extent by which commensal microbes are central to proper immune system development is demonstrated by the severely altered immune response in GF animals. These rodents suffer from massive impairment across all organs, including neurological and behavioral abnormalities,[42] reduced longevity,[43] altered metabolism,[44] impaired intestinal function,[45] and impaired immune responses.[46] Moreover, the immune system in GF mice is impaired and includes smaller Peyer's patches, fewer plasma cells, fewer intraepithelial

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lymphocytes, impaired antimicrobial peptide production, and immunoglobulin A (IgA) secretion, as well as imbalanced T-cell populations, with a skew toward a Th2 state, and compromised innate lymphoid cells (ILCs) function. GF mice are developmentally set but due to the lack of incoming microbes and their ability to shape and optimize biological functions, GF mice have a greater susceptibility to infections.[47] Once microbes are introduced, they trigger immune system maturation. Examples of these include the immune modulation of *Clostridium* consortia driving gut-regulatory T cells,[3,48] the mouse segmented filamentous bacteria that drive Th17 immune response,[4,49] as well as multiple individual gut bacteria affecting a myriad of immune phenotypes.[5,50] Immune-commensal dependencies are also observed in specific pathogen-free conditions. For example, studies show that the commensals promote a crucial innate myeloid–lymphoid crosstalk essential for immune homeostasis. Following macrophages' sensing of commensals, ILCs drive the production of granulocyte–macrophage colony-stimulating factor, a key determinant of myeloid lineage differentiation.[51]

In focusing on the impact of healthy host–microbiome interactions on the immune response, the complexity of the gut microbiota is a mix of both redundant and specific microbial functions. Each bacterial strain often elicits a unique immune signature; yet, many of the immune effects are shared across strains and species even from distantly related phylogenies. The immunomodulatory effects of microbes do not seem to be encoded in their phylogenetic origin and even strains from the same species could exert different immune effects on the mammalian host. This emphasizes the complexity and importance of the gut microbiota effects on the mammalian host and ensures robustness for loss of species due to physiological or environmental perturbations. This robustness can be obtained by maintaining a diverse collection of species.

5. Gut Microbe–Host Interactions Are Optimized by Their Biogeographical Distribution

Our intestinal system represents a gateway for outside microbes and food to enter our body. As such, the intestine is a highly vulnerable area and must have developed powerful ways to clear and prevent unwanted molecules from entering the body. One possible way to enable such a protection is by spatial colonization patterns of the gut microbiota. Microbes in nature live in complex, multispecies communities in which bacteria exchange information and exchange metabolic products and signals.[52,53] However, microbial communities adapt to their physical environment and availability to nutrients. For example, the mouth and rectum have a slightly higher oxygen concentration compared to the middle of the small intestine or the cecum area. Gut microbial composition, in terms of aerobes and anaerobes, most likely also adapt to these differences. Other factors influencing microbial biodistribution in the host include pH, proximity to host cells, neighboring microbes, and more. While some data are available for the microbiome spatial organization in ants,[54] our understanding of the spatial organization of microbial species in human body niches, and its importance to our health, is still in its infancy.[55–57] How does host–microbe crosstalk contribute to the establishment of ecological niches as well as the formation of interactions between neighboring species? What is the functional importance of the microbial spatial distribution? For example, studies have shown that the topological distribution of microbes in the tonsils may determine the efficacy of antibiotic treatment during acute tonsillitis.[58] Intratumor bacteria may impact tumor resistance to chemotherapy by selectively degrading it.[59] Understanding the spatial relationships among bacteria and topological cues that control the formation of microbiome communities in a given tissue is likely to become another future area of research required to better understand how they assemble, exchange metabolites, and interact with the mammalian host.[60–62] Ultimately, and in line with the ambition to generate new treatment regimens for lifestyle-related diseases using microbial intervention, the impact of microbial biogeographical localization on host physiology and disease merits further studies.[56,62–64]

6. What Is in It for the Microbes Residing in a Human Body?

In animals with a regulated body temperature (homeothermic), microbes benefit by reducing numerous metabolic needs compared to that of "cold-blooded" (poikilothermic) creatures such as worms or snakes. As such, mammalian commensals thrive on the specialized atmospheric and metabolic microenvironments created by their host.[65] In addition, some bacteria have been shown to thrive on host-derived epithelial cells and mucus;[66] the availability of niche-specific conditions, such as periepithelial oxygen gradients, supporting some microbial strains;[67,68] and protection from pathogenic invasion by host-derived factors such as antimicrobial peptide secretion,[69] mucus layer barrier function,[70] and IgA secretion.[71]

Collectively, the above examples capture the mutualistic benefit that both the host and its residing microbes encounter in multiple facets. This interplay is highly dynamic and must be on constant alert to avoid failure and collapse of organ and cellular function that may impair the conditions mutually beneficial for the eukaryotic and prokaryotic partners. Absence or alterations in these communication channels result in severe and long-lasting adverse effects for the holobiont.[8,46,72]

7. Altered Homeostasis May Elicit Antagonistic Gut–Microbe–Host Interactions

In contrast to the above mutually beneficial host–microbiome interactions, increasing number of "multifactorial" diseases are shown to feature altered "dysbiotic" microbiome configurations. These include allergies, asthma, inflammatory bowel diseases, T1D, and even cancer. In some of these studies, the dysbiotic microbiota or even distinct members in them contribute to disease pathogenesis.[73–81] Hence, much research is needed to better understand, for example, how gut microbes maintain a metabolic homeostasis in the gut while at the same time support host immune and epithelial cells.

An example of a "dysbiotic" microbiome configuration driving an antagonistic vivarium-dependent activity is featured in mice

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deficient in the immune-sensing Nod-like receptor NLRP6. These mice have been shown to harbor a dysbiotic microbiome[82] at some vivaria, which contributes to modelsof autoinflammation[82] and cardiometabolic disease.[83] Microbiome transfer experiments suggest that dysbiosis in these mice is host genotype- and surrounding microbiome-dependent rather than driven by husbandry effects.[72,84–88] Moreover, the dysbiotic microbiome in NLRP6-deficient mice features an inherent dominance over the indigenous wild-type (WT) gut microbiome as, upon transfer, it takes over the niche and transmits disease susceptibility into recipient WT mice.[82,83] Importantly, similar dominance of disease-associated microbiome configurations has been reported in other dysbiotic animal models,[4,89] suggesting that this "hostile dominance" may be a common feature of some disease-transmitting microbiomes. Interestingly, this mutualistic host–microbiome determination of the common niche was determined by differential molar combinations of signatures of metabolites in healthy and dysbiotic microbiomes, which impacted the host antimicrobial profile and thus the "supportive social environment" nurturing the healthy or the dysbiosis ecosystems. The dysbiotic microbiome was able to "hijack" this communication channel, thereby creating a metabolite environment that conferred a competitive environment over the invaded healthy microbiome. Notwithstanding this mechanistic example of host–microbiome relationships, it only represents an example and more contexts of antagonistic microbiome dominance need to be mechanistically explained in future studies.

8. Industrial Revolution, Urbanization, and Loss of Social Interactions Are Detrimental for Microbiome Diversity and Richness

The drastic recent man-made changes in our environment have triggered unwanted changes in the "healthy" microbiome and potentially predisposed affected populations to a variety of "modern diseases" including the effects of modernization on microbiome diversity. Millions of years of evolution have been modulating the lifespan and genetic shape of the nonhuman primates and nonindustrial humans. The introduction of the ability to use fire, to predigest, and the introduction of agriculture techniques radically altered our diet and lifespan. In the last 200 years, additional changes such as high social, economic, and public health advances have enabled industrial humans to distance themselves farther from nonindustrial humans than those humans from other primates, impacting life habits, health status, and lifespan.[90] These rapid changes are less to do with genetics and are believed to be driven by profound environmental changes occurring within a small evolutionary timescale. Indeed, considerable alterations in reducing labor-saving devices, introduction of antibiotics, altered nutritional habits, rapidly changing housing conditions, and delivery by cesarean section may account, in part, for the critical components of this drastic and rapid change in the human environment. From the holobiont perspective as a functional unit, the indigenous microbes must have undergone simultaneous drastic changes in composition, diversity, and function over this short period of time.

Indeed, recent work on the microbiome composition and diversity of metabolite production of human hunter–gatherers, the Hadzas of Tanzania, support this association.[91] Hadzas have dramatically higher gut microbiome richness and biodiversity as compared to urbanized "modern" human controls. Further comparisons show no evidence of *Bifidobacterium* but instead enrichment in *Prevotella*, *Treponema*, and unclassified Bacteroidetes, as well as a peculiar arrangement of Clostridiales taxa in this indigenous human population, potentially facilitating Hadzas' ability to digest and extract valuable nutrition from fibrous plant foods.

Interestingly, whereas the Hadza group produced more of the short-chain fatty acid (SCFA) propionate, the "modernized" groups produced more of the SCFA butyrate.[92] While propionate is transported to the liver for gluconeogenesis, butyrate, among its numerous functions, also activates the longevity hormone, FGF21,[93] suggested to regulate the AMPK–sirtuin1–mTOR pathway. This interesting divergence in microbiome communities results in one being dedicated to promotion of daily survival, while the other features an ability to potentially support longevity genes potentially connected to a longer lifespan. Indeed, a recent longevity study[94] demonstrated that the Hadza population has a longer expected lifespan than other human beings living in urban societies, possibly contributed by changes in the lifestyle and constrained access to nutrients, coupled with a rich and diverse microbiome. Notwithstanding these associations, they merit further validation and mechanistic elucidation.

Other microbiome coevolutionary adaptations responding to alterations in dietary composition include exposures to a low-nutrient environment, in which microbes are selected for an ability to generate energy with high efficacy. In contrast, exposure to an energy-rich environment selects microbes with an ability to execute different functions, apart from being digestive in nature, which putatively can be afforded due to excess of energy. Today, excess of food and energy including an excess intake of sugar-rich drinks have generated a new intestinal environment, flooded in energy, which is gradually altering the microbiome composition and diversity toward new configurations. The full implications of this massive temporal change are not yet understood but may result in the altered microbiome community becoming less diverse, a feature that is associated with predisposition to a number of "multifactorial" illnesses.[90,95] While further studies are required to fully understand the effects of modernization on microbiome composition, functions, and crosstalk with the eukaryotic host, it may enable to better understand the increase in modern diseases and their unique and person-specific pathophysiological driver mechanisms.

9. Conclusions and Prospects

In this review, we provided snapshots illustrating how host–microbiome interactions, driven, like higher human inter-relationships by cooperative versus antagonistic community structure and activity, may influence host physiology, health, and risk of disease (Figure 1). We are only at the beginning of mechanistically understanding these host–microbe interactions and their impact on human health. Uncovering how dietary, social, and other lifestyle-related factors drive the continuous and drastic alteration in the "average" composition of our internal commensal microbes may shed important light on how modernization has impacted the pathogenesis of multiple "modern" diseases

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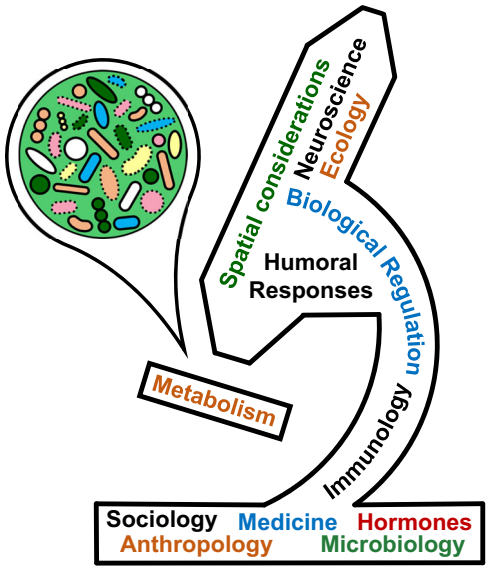

Figure 2. Multidisciplinary approaches to study the holobiont. There is a need for a variety of research disciplines and approaches for a better understanding of host–microbiome interactions. The different disciplines are shown as part of the microscope through which the microbiome is studied.

such as obesity, diabetes, cancer, and neurodegeneration. Likewise, reaching a mechanistic understanding of the resultant effect on microbe–microbe and host–microbe molecular interactions, by combining studies from different disciplines (**Figure 2**), may delineate how these contribute to disease formation, and identify a new microbiome therapeutic targets for common "multifactorial" diseases. With a better understanding of the person-specific factors driving variabilities in microbial composition and function between humans, we may begin to decode the microbial contribution to individualized health traits and to unique phenotypes in different individuals suffering from common diseases (Figure 2). Such precision-medicine understanding of human health may enable to harness host–microbiome features in diagnosing, stratifying, preventing, and treating common human diseases.

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Conflict of Interest

E.E. is a consultant at DayTwo and BiomX.

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