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The Gut Microbiome–Human Body Symbiosis: Relevance of the Ubiquitous Microbial Community on Health and Development, Part 2

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ABSTRACT

The human gut microbiome, comprising a range of microbial species (~100 to 1,000), is an extremely malleable ecosystem. It originates around the time of human birth and evolves as the infant grows until it matures into the relatively stable adult gut composition. Through this dynamic evolution, the composition of the gut microbiome is influenced or altered by factors such as diet, environment, mode of birth, genetics, infections, and medications. Strong associations between such alterations (dysbiosis) and diseases have led scientists to develop therapies that target a malfunctioning gut. Research is now focused on the microbiota or their associated metabolites as potential therapies. Treatment options explored include prebiotics, probiotics, postbiotics, synbiotics, fecal microbiota transplants, and live biotherapeutic products. The gut microbiome is not a panacea for all health issues; rather, it is part of a large network of interconnected operating systems within the human body. As communicators of scientific data, medical writers play a vital role in educating the public on the merits and limitations of gut microbiome therapeutics. Popular discourse, however, can be influenced by misinformation. With the ever-growing influence of social media, the lay reader must learn how to critically appraise the health information propagated by these sources. This second part of the gut microbiome series explores the association of the gut microbiome with human disease and the role that social media plays in influencing the popular perception and understanding of the importance of the gut microbiome. Approved and experimental therapies using the gut microbiome will be discussed.

Social media pundits and science communicators are extremely important in monitoring the quality and integrity of discourse on the impact of the gut microbiome on human health.[1-3] Microbiome researchers set out to confirm the association of gut dysbiosis (Box 1) with many chronic diseases. However, a decade later, it is becoming increasingly difficult to conclusively link gut dysbiosis with specific diseases due to the vast heterogeneity of the human microbiome.[4] The gut microbiome is so vital to our existence that it is referred to as the second genome.[5] Genetics and the living context define the healthy equilibrium between the gut microbes and the body.[5,6] The dynamic evolution of the gut microbiome from birth to adulthood ensures diversity in the

Box 1.

Microbiome
A microbiome is an ecosystem of microorganisms (eg, bacteria, viruses, phages, fungi, archaea), their genes, and metabolites in a particular environment.

Microbiota
Microbiota are microorganisms (eg, bacteria, viruses, fungi, archaea, and phages) that live in a particular environment.

Dysbiosis
Changes to the composition of the gut microbiome (eg, function and taxonomy) cause dysbiosis. Drastic disturbances to the gut microbial balance are linked to inflammatory bowel disease, obesity, type I diabetes, asthma, autism spectrum disorder (ASD), and allergies. Gut dysbiosis causes inflammation and immune reactions.

Epigenetics
Epigenetic changes modify gene expression by acetylation or methylation of DNA in the absence of changes (eg, insertions, deletions, duplications) to the DNA sequence.

Interactome
An interactome is a biological community that functions on the basis of an interactive network of human genes, epigenetic modulation, environmental features, and the microbiome.

Metabolome
A metabolome is the comprehensive collection of metabolites in a system (eg, body, cell, organ).

Xenobiotics
Xenobiotics are chemicals (eg, industrial pollutants, drugs, fertilizers, or pesticides) that are not naturally found within a biological system and are metabolized by microbes.

Circadian cycle
A circadian cycle is a 24-hour cycle that governs the metabolic, physical, behavioral, and mental signaling networks within the body.

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gut microbial community.[7,8] The gut microbiome is part of a complex network or interactome consisting of the metabolome (Box 1), the gut–organ axes, environment, genetics, and epigenetics.[9] A disruption to any part of the interactome could alter the crosstalk and result in disease.[9] Diseases manifest when there is a shift or change to the microbial diversity in gut microbiota (dysbiosis) due to infections, stress, intake of antibiotics and other medications, age, exposure to xenobiotics (Box 1), seasonal changes, circadian rhythms, an unhealthy diet, industrialization, exposure to pets, use of chemical disinfectants, or type of birth.[10,11] This review will discuss ways in which gut dysbiosis affects health and how the gut microbiome can be manipulated as a target for promising new treatments.[4,12,13] As medical writers, we should proceed cautiously when promoting the health benefits of the gut microbiome.[14,15] By reporting evidence-based information, medical writers should also have an obligation to counter social media's exaggerated claims of the gut microbiome as a panacea of health.[2,3,16]

THE GUT MICROBIOME IN DISEASE

In healthy humans, there is a bidirectional crosstalk between the gut microbiota, the immune system, and the intestinal mucosal surface.[10] In a disease state, this crosstalk is affected.[10] It is unclear if gut dysbiosis either causes or is caused by diseases.[9,12] Gut dysbiosis manifests as a result of an unhealthy diet, environmental changes, type of birth, and antibiotic use, among other factors.[17] Gut dysbiosis favors the proliferation of pathogenic gut bacteria.[9,10] This results in inflammation that triggers an immune response.[9,10,17,18] Inflammation increases the permeability of the intestinal epithelial membrane.[10,18] This allows pathogenic gut microbes and metabolites to translocate through the membrane and travel via the systemic circulation and the respective gut–organ axes to target organs.[9,17] The circulation of these pathogenic gut microbes and their metabolites can all activate or enable epigenetic modifications. Individually or jointly, these factors can impact human disease (Figure 1).[10,11,17-20] The role of gut dysbiosis in diseases will be elucidated in this section.

Metabolic Syndrome

Metabolic syndrome encompasses nonalcoholic fatty liver disease (NAFLD), diabetes, obesity, hypertension, and cardiovascular disease.[6,8,12,21-24] Antibiotic use in infants appears to be associated with the risk of developing these diseases in later life.[9,25-29] Obesity in metabolic syndrome results in part from gut dysbiosis from a high-fat, sugar-concentrated, and low-fiber Western diet, genetics, sedentary lifestyle, maternal gestational diabetes, and the circadian cycle (Box 1).[8,12,23,24,30-32] In patients with type 2 diabetes (T2D) (Table 1), gut dysbiosis is associated with a Western diet, obesity, persistent inflammation, and an increase in the concentration of branched-chain amino acids in the serum.[12,23,24,31]

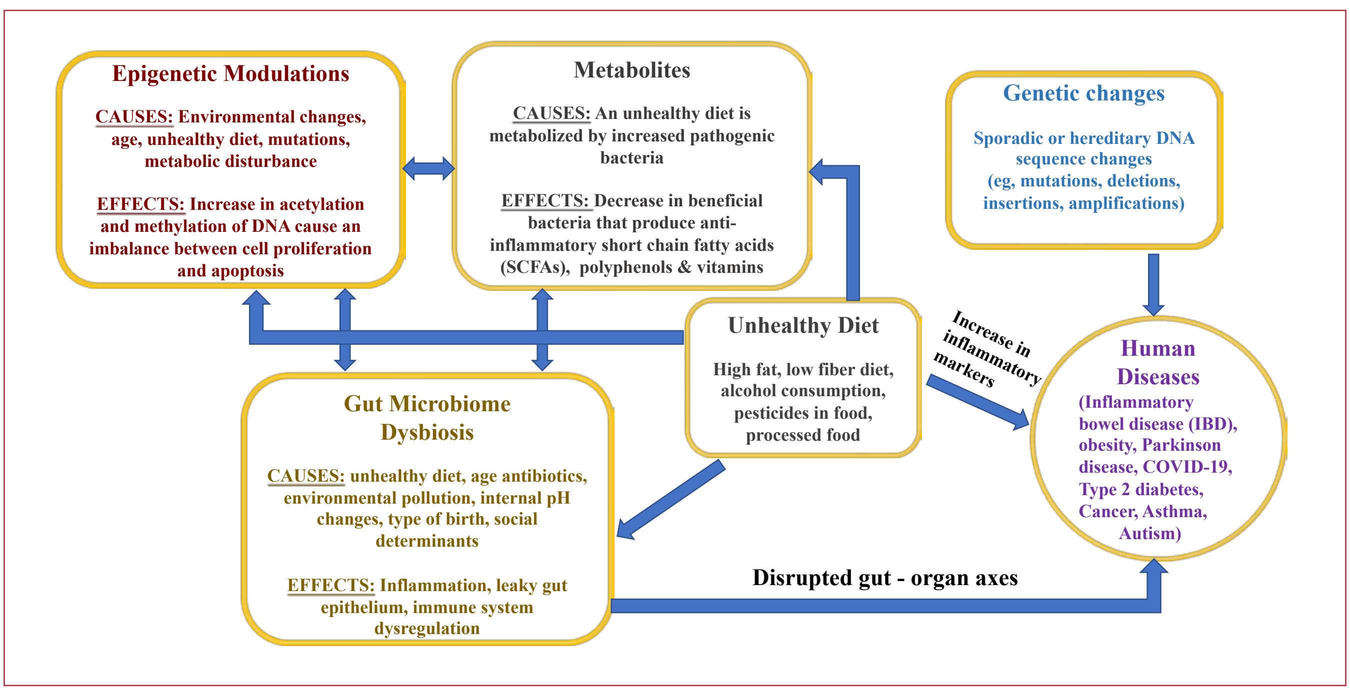

Figure 1. Potential Pathways to Human Disease. Interconnected pathways associated with human disease. Dysbiosis results from epigenetic modulations, pathogenic microbes, and metabolites released from an unhealthy diet, use of antibiotics, and environmental triggers, among others. Gut dysbiosis along with an unhealthy diet and gene sequence changes can disturb the usual homeostatic balance in the body, which is linked to disease.

Cardiovascular Disease

Studies, although inconsistent, have found that high plasma trimethylamine N-oxide (TMAO) levels are associated with a risk of cardiovascular disease.[8,24,42,43] This microbial metabolite is the byproduct of a low-fiber, meat-oriented Western diet.[8,24,42,43]

NAFLD

In NAFLD, gut dysbiosis or fat accumulation in the liver inflames the liver and other organs comprising the gut–liver axis. Inflammation increases intestinal wall permeability that allows pathogenic microbes (Table 1) and their metabolites to reach the liver through the portal vein or systemic circulation.[8,38,44,45]

Gastrointestinal Diseases

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is an umbrella term for the group comprising indeterminate colitis, ulcerative colitis, and Crohn disease.[24,46] Research has convincingly shown microbial perturbations in the gut in those with IBD, although it is not clear if gut dysbiosis is a cause or an effect of IBD.[24,46,47] IBD has been associated with gut dysbiosis, inflammation of the intestinal mucosa, lesions in the gastrointestinal tract, genetics, environmental influences, and immune system perturbations.[9,15,24,46,48]

Malnutrition

Inadequate or overnutrition causes malnutrition. Dietary supplements alone rarely correct malnutrition. However, research has shown that a diet of peanuts, bananas, and chickpeas may modify the gut microbiomes of malnourished children by encouraging the growth of age-specific bacteria.[49-51]

Neurological Diseases

It has been postulated that gut microbes exert an influence on emotions, processing capabilities, and even behavior.[52-54] Research now shows associations between gut dysbiosis and mental disorders, such as anxiety, epilepsy, autism, depression (Table 1), sleep irregularities, Parkinson disease, and Alzheimer disease.[6,36,55-59] The gut microbiota communicates with the brain through the gut–brain axis.[60] Intestinal microbiota translocate across the permeable intestinal wall and migrate to the brain where toxic metabolites, inflammation, and oxidative stress damage the integrity of the blood–brain barrier.[61]

Dermatological Diseases

Dysbiosis in the gut–skin axis is associated with psoriasis, acne vulgaris, alopecia areata, and atopic dermatitis, among others.[62-66] Diet, genetic susceptibility, and hygiene influence the bidirectional communication within the gut–skin axis.[65,67-70]

Respiratory Conditions

Asthma

The risk of developing asthma has been attributed to a Western lifestyle, the mode of birth (eg, cesarian section), industrialization, and the use of antibiotics.[24,71,72] Although genetics may be involved, environmental changes that reduce gut microbial diversity increase the susceptibility to airway inflammation.[72,73] Changes in the gut microbiome (Table 1) are reversible and dynamic. Replenishing the gut microbiome with health-promoting bacterial strains helps to reduce airway inflammation.[24,73]

COVID-19

The SARS-CoV-2 virus infects the gastrointestinal (Table 1) and respiratory tracts of humans with associated inflamed lungs and colon damage.[18,74] Fecal sampling studies have shown reduced gut microbial diversity, decreased commensal species that maintain intestinal equilibrium and regulate host immunity, increased bacteremia-associated bacteria, and other distinct differences in infected patients compared with healthy individuals.[18,34,75]

Cancer

The role of the gut microbiome in colorectal cancer and gastrointestinal cancer has been documented.[10,41,76-78] Genotoxins secreted by *Escherichia coli* (colibactin) and

Table 1. Microorganisms Associated With Diseases

Diseases	Causative Bacteria or Microorganisms
T2D[12,33]	↓ *Faecalibacteria*, ↓ *Bacteroides*, ↓ *Akkermansia*, ↓ *Bifidobacteria*
Obesity	↓ *Bacteroides*,[23,24] ↓ *Akkermansia*[24]
Atopic Asthma	↓ *Akkermansia*,[24] ↓ *Lachnospira*, ↓ *Faecalibacterium*[24,25]
ASD[24]	Bacteria: ↑ *Corynebacterium*, ↑ *Lactobacilli*, ↑ *Colinsella* Fungus: ↑ *Candida*
COVID-19[34,35]	Bacteria: ↑ *Actinomyces viscosus*, ↑ *Clostridum hathewayi*, ↑ *Bacteroides nordii*, ↑ *Enterococcus*, ↑ *Enterobacteriaceae*, ↓ *Faecalibacterium prausnitzii*, ↓ *Roseburia*, ↓ *Lachnospiraceae*, ↓ *Eubacteria* Fungi: ↑ *Aspergillus flavus*, ↑ *Candida albicans*, ↑ *C. auris*
Depression[36]	↓ *Bifidobacteria*, ↑ *Streptococcus*, ↑ *Klebsiella*
NAFLD[37]	↑ *Enterobacteriaceae*, ↑ *E. coli*,[38] ↓ *F. prausnitzii*
Cancer	↑ *Helicobacter pylori*, ↑ *Fusobacterium nucleatum*, ↑ *Bacteroides* fragilis, ↑ *Shigella flexneri*,[39,40] ↑ *Escherichia coli*[40,41]

↓ Reduced microbial levels; ↑ Increased microbial levels; ASD, autism spectrum disorder; NAFLD, nonalcoholic fatty liver disease; T2D, type 2 diabetes.

Morganella morganii (indolimine) act in distinct ways to damage DNA and cause genomic instability that gives rise to benign and metastatic tumors.[41,77] Pathogenic bacteria (eg, *Fusobacterium nucleatum, Bacteroides fragilis, Shigella flexneri*) inhibit the immune response to tumors and potentially contribute to carcinogenesis.[41,77]

TREATMENT STRATEGIES

The purpose of gut microbiome therapy is to restore the appropriate age-related microbial diversity associated with optimum health (eubiosis).[17,26,79] The gut microbiome can be a target of treatment, or it can serve as a source of biotherapeutics.[80] As clinical biomarkers, microbial signatures associated with symptoms can indicate the effectiveness of personalized treatment, for example in COVID-19 or neurovascular disease.[4,35,81-83] Researchers are looking into ways to modulate the impact of therapies by manipulating the gut microbiota.[10,77] The heterogenous gut microbiota can change the potency of drugs and their subsequent actions by binding and altering their conformation, metabolizing them, modifying liver or mucosal barrier function, or regulating gene expression.[10,77] This section discusses different forms of experimental microbiome therapies. Large-scale clinical studies are necessary to verify their impact on human health. Currently, fecal microbiota transplant (FMT) is the only US Food and Drug Administration (FDA)-approved microbiome therapy for *Clostridioides difficile* colitis infections.[4]

Prebiotics

Prebiotics are fermented, nondigestible food ingredients that are selectively utilized by host microbes and provide health benefits by enhancing the growth of one or more bacteria in the colon (Table 2).[12,18,60,81,84,86] Prebiotics regulate enzymes that modulate xenobiotics, inhibit pathogen growth, and modulate immune responses.[18,81,86] Although preliminary studies reveal positive effects of prebiotics in depression, colorectal cancer, schizophrenia, anxiety, and stress, large randomized controlled studies are required to confirm these positive effects.[12,52,87-90] Prebiotics can be administered directly to the skin and vagina or taken orally to reach the intestines.[18]

Nutrients or Dietary Interventions

Diet plays an important role in shaping gut microbiome composition.[9,17,19,24] In premature infants, breastmilk, human donor milk, and formula impact gut flora and the developing immune system.[91,92] Indigestible dietary fiber and complex carbohydrates (human milk oligosaccharides) are metabolized by commensals in the large intestine to produce short chain fatty acids (SCFAs) that help to prime the immune response and reduce inflammation in the host.[34,93]

Probiotics

Probiotics are defined as "live microorganisms that, when administered in adequate amounts, confer a health benefit to the host" (Table 2).[12,81,94] Their use is still in the experimental stage. Large-scale studies are required to confirm the positive impact of probiotics as treatment.[14,86] Most probiotics are bacteria and yeast.[14,46,86,95,96] Among the panoply of effects, probiotics can prevent colonization by pathogenic bacteria, improve gut microbiome diversity, regulate the immune system, and prevent allergies.[12,17,18,91,97,98]

The FDA and European Food Safety Administration consider live biotherapeutic products, probiotics used to treat specific diseases, as drugs that require stringent regulations before they can be sold in the market.[12] Beneficial effects of probiotics have been observed in diabetes, depression, cancer, ulcerative colitis, autoimmune arthritis, multiple sclerosis, and rotavirus diarrhea.[12,17,18,36,87,91,97-105] In premature infants, probiotics modify gut microbiome diversity that appears to improve host immunity and reduce feeding intolerance as well as mortality.[15,91]

Most probiotics are considered safe as food supplements although patients who are immunocompromised should not use them.[39,86] Probiotics are commonly found as ingredients in fermented products, for example, yogurt, cheese, and fermented soy.[86,94] The efficacy of probiotics depends on the stage of the disease when the probiotic is administered, the dosage, dietary modifications suited to the requirements of the introduced probiotic, the overall health of recipients, and the duration of treatment.[18,24,81] As part of a personalized approach to treatment, identifying the microbial signature of the gut will influence the selection and efficacy of the appropriate probiotic.[24,91]

Synbiotics

Synbiotics are defined as "a mixture comprising live microorganisms and substrate(s) selectively utilized by host microorganisms that confers a health benefit on the host."[94] For example, the prebiotics fructooligosaccharides enhance the growth of probiotic Bifidobacteria, which help to prevent necrotizing enterocolitis, COVID-19, and antibiotic-associated diarrhea.[57,81,106] Probiotics combined with wheat aleurone (dietary fiber) help to reduce the risk of colon cancer by improving intestinal health.[86] Synbiotic treatment has been effective in treating T2D, NAFLD, depression, and irritable bowel syndrome.[81,87,99,107-109] Prebiotics supplement the action of probiotics to inhibit the activity of angiotensin-converting enzyme-2 when they are used together in patients with COVID-19.[106] Combined use of prebiotics and probiotics appears to reduce symptoms of depression and anxiety.[52]

Postbiotics

Postbiotics are "a preparation of inanimate microorganisms and/or their components that confer a health benefit to the host" (Table 2).[21,94] Postbiotics are nontoxic, found in high concentrations, ubiquitous in the human body, stable when introduced into the circulatory system, and can be administered through multiple routes.[13,111,112]

Enterosynes

Enterosynes are diverse molecules that function as bioactive lipids or peptides, microbiota, hormones, immune molecules, and nutrients.[37] Strategies that target enterosynes could potentially treat diseases like T2D.[37]

Phage Therapy

Phages are viruses that infect bacteria.[13] Phage cocktails have been found to be safe for patients.[13] In a recent study, a combination of 5 phages had an immunosuppressive effect on patients with IBD, and in a phase I human clinical trial, phages suppressed Klebsiella pneumoniae, a common pathogenic bacterial strain in IBD.[112,113] Fecal virome transplantation studies have been deferred due to controversies over the safety of phages as therapeutic agents.[12] Large randomized, controlled studies are needed to confirm the impact of these new biomolecular therapies.[12,21,37,114]

FMTs

FMTs improve microbial diversity in a dysbiotic gut.[61,81] In FMT, preprocessed stool in a capsule or in liquid form is transplanted from a healthy donor into the colon of an individual with a disease.[12,17] In addition to microbiota, an FMT contains vitamins, SCFAs, and bile salts.[17] FMT therapy has shown promise in neurological conditions (eg, autism spectrum disorder, Parkinson disease), obesity, gastrointestinal disorders, blood disorders, diabetes, and liver diseases.[4,8,13,17,24,115-124]

In September 2022, the FDA approved FMT to treat *Clostridioides* (old name: *Clostridium*)[12] *difficile* colitis.[4] Additional approved therapies include Vowst, an oral drug containing fecal microbiota spores,[125] and Rebyota, a live microbiota-based FMT.[4,126]

The quality of the donor microbiome is an acknowledged risk of FMT. Donor selection depends on factors, such as the type of birth (caesarean vs vaginal), smoking history, and prior antibiotic exposure.[13,24,81,116] There is a risk, especially in patients who are immune-compromised, of transferring resident pathogens, multidrug-resistant bacteria, or infection via the donor microbiome.[13,24,81,116]

ROLE OF BIOMEDICAL WRITERS IN COMMUNICATING HEALTH INFORMATION

Enthusiasm for gut microbiome research has propelled a flurry of books, articles, and videos on the medicinal properties of foods, diets, and food-related therapies.[2,55,127] However, the promise (beneficial effects) and peril (harmful effects) of manipulating the gut microbiome have often been exaggerated and misinterpreted (Table 3).[16,127-130]

The social media landscape is a vast, fertile ground for the dissemination of information.[3] YouTube and TikTok are some of the sites where videos generate interest and find viewership. Many advocate home remedies while quoting purported beneficial effects of the bacterial constituents on our health. These benefits are claimed to be based on data from research studies.[16,129,130] Amid all the hype, it is necessary to approach gut microbiome-linked health information with caution (Table 3).[2,130] Social influencers and celebrities seek to promote gut microbiome-inspired therapies as part of the wellness industry.[3] Unfortunately, government

Table 2. Examples of Prebiotics, Probiotics, and Postbiotics[13,15,18,84,85,86]

Microbe-Associated Potential Therapies	Source	Examples
Prebiotics	Vegetables (eg, broccoli, onions), grains (wheat), fruits, nuts, or as purified dietary supplements.	Psyllium, oligosaccharides, fructooligosaccharides (eg, banana, chicory root, asparagus, garlic), human milk oligosaccharides, lactosucrose, xylooligosacharides, polyphenols, galactooligosaccharide, mannan oligosaccharide, resistant starch, polyunsaturated fatty acids, arabinooligosaccharides, dietary fibers.
Probiotics	Microbes in fermented foods (eg, kefir, yogurt), also available as nasal sprays or oral supplements.	*Lactobacillus rhamnosus*, *L. helveticus*, *L. casei*, *L. acidophilus*, *Streptococcus thermophilus*, *Lactococcus lactis*, *Enterococcus fecalis*, *L. bulgaricus*, *L. paracasei*, *L. plantarum*, *Bifidobacteria longum*, *B. bifidum*, *Bacillus coagulans*, *Faecalibacterium prausnitzii*, *Akkermansia muciniphila*, *Lactobacilli reuteri*, *L. brevis*, *B. breve*, *Bacteroides fragilis*, and *L. gasseri*.
Postbiotics	Nonviable microbial cells or cell fragments.	Cell byproducts (SCFAs), TMAO, cell components (eg, proteins, endo- and exopolysaccharides), enzymes, microbe-targeted toxins, bile acids, acetic acid, tryptophan, lactic acid, vitamins, peptidoglycans.

SCFAs, short chain fatty acids; TMAO, trimethylamine oxide.

Table 3. Recommendations for Responsible Dissemination of Gut Microbiome Research

Current Trends in Dissemination of Gut Microbiome Research	Suggestions for Medical Writers for Responsible Dissemination of Gut Microbiome Research
The lay public has limited awareness of the role played by the gut microbiome in gut health within the human body framework.[2,9]	The concept of the gut microbiome should be presented as a unique ecosystem of microbial communities that is indelibly interwoven within the cellular organization of each individual and evolves from the combined influence of the environment, diet, medications, social determinants, and industrialization.[9,12]
Disease results from a disruption in the biochemical network within an organ system. Research now indicates that diseases occur when associations between biochemical networks of different organ systems including the gut are disrupted.[9]	Association data should be interpreted to show that there is a complex interactome at work in a disease.[9] The biochemical network of the gut microbiome should also be considered as affected during disease along with the biochemical network of the affected organ.[9]
Microbiome hype is mediated by popular health articles and social media, including YouTube videos by celebrities with promises of instant cures from diseases.[1,3,16]	Plain language patient education materials and videos by trusted sources, such as scientists and health professionals, could help to educate the public on the advantages and disadvantages of manipulating the gut microbiome, thus preventing the spread of misinformation.[2,3]
The representation of the gut microbiome in the public domain involves opposing concepts. For example, personalized nutrition companies confidently project gut microbiome therapies as a panacea for good health. In contrast, they provide disclaimers that the results obtained using their personalized nutrition technology should not be considered in place of a medical expert's opinion.[5]	Companies should explain the effects of the gut microbiome on human health to enable the consumer to make an informed decision on accessing personalized gut microbiome treatment for a given disease.[5]

websites or research articles are dense in information and are not reader-friendly for the lay public.[2] The lay public is not inclined to absorb information from these resources, especially when social media provides this information in attractive formats.[2,3] Medical writers, in their role as educators, should understand the current information landscape and utilize popular channels of public information to communicate effective and credible information to the lay public.[3]

It is the responsibility of science writers, medical communicators, and health experts to interpret and disseminate evidence-based factual information about popular health trends, such as the use of pro-, pre-, or postbiotics so that the public can make educated decisions regarding their use.[2,3] In this way, medical writers, health writers, and communicators can influence the discourse of scientific information in the public domain.[2,3] The lay public, in turn, will learn to recognize and trust the information from reliable science communicators and websites.[2,3] This will improve the influence of credible science in the public domain.

CONCLUSION

Microbial signatures could serve as personalized biomarkers to distinguish a healthy individual from someone with a disease.[12,59,82,83] And yet, there has been limited success in treating diseases on the basis of this core belief. This does not diminish the value and importance of the gut microbiome. On the contrary, research has revealed that the gut microbiome is one of many players in the complex interconnected biological network (interactome) within the human body.[19,131] Similarly, we can foresee a future of personalized treatment in which disease is always assessed simultaneously by a cohort of physicians specialized in fields related to the interactome that includes the gut microbiome. When data from large randomized controlled studies are positive and consistent on the benefits of the gut microbiome as treatment, then the lay public can utilize this information with confidence. Science writers, medical communicators, and health experts have a responsibility toward the public in interpreting and disseminating vital information on the impact of the gut microbiome on human health and well-being.

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