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The Gut Microbiome–Human Body Symbiosis: Relevance of the Ubiquitous Microbial Community on Health and Development, Part 1

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ABSTRACT

There appears to be a collaborative nexus between the human body and its resident microbes. Research shows strong associations between this parallel universe of microorganisms and our overall health, immunity, and behavior. The human microbiome consists of microbes that flourish in different parts of the body. Our gut with all its projections spans nearly 7 kilometers in length and contains the largest number of microorganisms within the human body. An imbalance in the gut microbiome is strongly associated with allergies, metabolic diseases (eg, diabetes, obesity), neurological conditions (eg, depression, autism), respiratory diseases, liver diseases, and cancer. The development of the gut microbiome is a dynamic process that begins either during gestation or at birth and continuously evolves with human growth into adulthood. The gut microbiome is part of an intricate metabolic and signaling network in the human body. It communicates through biochemical pathways or axes with the skin, brain, lungs, kidneys, breast, and liver. A key motivation behind gut microbiome research is to confirm the cause-and-effect role of the gut microbiota on host health homeostasis. Today, gut microbiome research is generating excitement due to its potential to prevent and treat several interrelated health conditions. Conclusive evidence of the role played by the gut microbiome on human health will furnish new avenues of treatment and better insights into the influence of diet, environment, antibiotics, and genetics on the body. This article, the first of a two-part review, will discuss the relevance of the gut microbiome and its prominent constituents, the developmental trajectory of the gut microbiome from infancy to adulthood and its mutualistic relationship with the human host.

Today, medical research is dominated by an overwhelming interest in the human microbiome.[1] Because advances in health and medicine are of genuine public interest, results related to microbiome research are popular. In North America, there is a hype about the microbiome where nearly 94% of articles discuss only health benefits, whereas very few articles provide critical assessments or limitations of microbiome research.[2] Microbiome is a term that refers to the ecosystem that comprises genes, metabolites, and associated products of bacteria, fungi, viruses, phages, and archaea (Box 1).[3-7] There is a symbiotic relationship between human cells and the microbial community that dwells in the human body.[8] In humans, there are approximately 39 trillion microbial cells, encoding nearly 20 million microbial genes.[3,9-12] In contrast, human bodies with approximately 30 trillion human cells possess a little more than 20,000 human genes.[12-14] This vast difference of a factor of 10^2 to 10^3 in microbial gene number has an impact on immunity, behavior, and health in humans. Although studies on the effects of the microbiome on human health have been around for more than 50 years, a dedicated human microbiome project was initiated in 2007 by the National Institutes of Health to

Box 1.

Microbiome
An ecosystem of microorganisms (bacteria, viruses, phages, fungi, archaea), their genes, and metabolites in a particular environment.

Microbiota
The microorganisms living in a particular environment, which include bacteria, viruses, fungi, archaea, and phages.

Dysbiosis
Changes to the composition of the gut microbiome (eg, function and taxonomy) cause dysbiosis as presented in a disease state. Drastic disturbances to the gut microbial balance are linked to diseases, such as inflammatory bowel disease, obesity, type I diabetes, asthma, autism, and allergies. Gut dysbiosis causes inflammation and immune reactions.

Alpha Diversity
The intraspecies diversity in a particular environment in an individual.

Vertical Transmission
Transfer of bacteria and genes directly from mother to child

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understand the physical and genetic structure of the microbiome.[1,4,15] The first phase of this project studied the composition of different microbiomes (eg, skin, buccal mucosa, gut, feces, vaginal wall, tongue, outer ear cavity, and other sites) in the human body.[15] A second integrative human microbiome project is studying the impact of 3 conditions–prediabetes, inflammatory bowel disease, and pregnancy–on the dynamic interaction between microbiomes and the human body.[4,15] There is evidence of biased reporting of gut microbiome benefits on human health. By reporting results before they have been verified in large sample studies or randomized controlled trials, the public may be misled about the impact and benefits of the gut microbiome on our health.[16,17] The following evidence-based review aims to provide a balanced overview of the gut microbiome and its role in the human body.

RELEVANCE OF THE GUT MICROBIOME IN THE HUMAN BODY

The gut or intestinal microbiome accounts for 99% (~ 1,000 to 4,500 species) of the entire microbial flora in the human body (Table 1),[5,11-13,18,19] making it the densest organ of metabolism on our planet. Research has demonstrated the significant role of the gut microbiome in immune system maturation, vitamin production, energy production from dietary components, breakdown of complex sugars from plant-derived products and human milk, protection of the body against pathogenic bacteria, maturation and development of epithelial cells, and neurotransmitter production to facilitate communication with the brain.[20-22] Processed foods, high-fat diet, high- protein diet, low-fiber food, antibiotics, alcohol, and diseases cause inflammation and create an imbalance in the composition or dysbiosis of the gut microbiome.[23,24] Gut dysbiosis (Box 1) appears to be associated with long-term impacts on the individual's health in the form of allergies (eg, hay fever), gastrointestinal diseases (eg, inflammatory bowel disease [IBD], Crohn's disease), metabolic diseases (eg, obesity, diabetes, and cancer), neurological conditions (eg, depression, autism, Alzheimer disease), and respiratory tract infections (Figure 1).[4,20,25,26]

ORIGINS OF THE GUT MICROBIOME

The First Stage: Seeding

The development of the gut microbiome is a dynamic process.[27] Two theories explain the seeding of the gut microbi-

Table 1. Types of Microbiota in the Gut

Bacteria		Fungi		Viruses and Bacteriophages		Archaea
Major Phyla (Term Infants)	**Major Phyla (Preterm Infants)**	**Children**	**Adults**	**Infants**	**Maternal Gut**	*Methanobrevibacter smithii* *Methanosphaera stadtmanae*
Proteobacteria *Firmicutes* *Actinobacteria* *Bacteroidetes* *Verrucomicrobia*	*Firmicutes* *Actinobacteria* *Bacteroidetes*	*Aspergillus* *Tremellomycetes*	Phyla *Basidiomycota* *Ascomycota* Genera *Saccharomyces* *Penicillum* *Aspergillus* *Candida*	*Myoviridae*, *Podoviridae*, *Microviridae*, and *Siphoviridae* families	*Microviridae* *Circoviridae*	Order Methanobacteriales

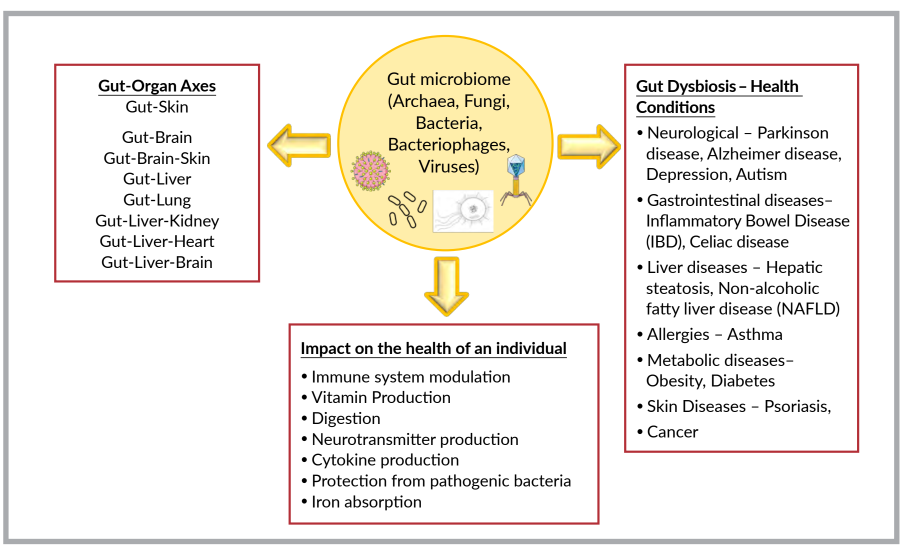

Figure 1. The relevance of the gut microbiome in the human host. The 3 main roles of the gut microbiome are outlined in the figure. Parts of the figure were drawn by using pictures from Servier Medical Art. Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/). Archaea cells icon by SwissBioPics https://www.swissbiopics.org/ is licensed under CC-BY 4.0 Unported https://creativecommons.org/licenses/by/4.0/.

ome in humans.[8,23,28] Bacteria initially colonize the immature gut of infants followed by viruses and fungi.[23,29,30]

Sterile womb hypothesis. This hypothesis states that the uterus of a pregnant person is a sterile environment, and microbial colonization of the fetal gut begins at birth during labor.[8,31,32] When the amniotic sac ruptures in a vaginal birth, the fetus is exposed to and enveloped by the mother's vaginal microbiome as it makes its way through the birth canal. Babies born via elective cesarean section have a gut microbiome that resembles the mother's skin microbiome.[3,8,13,33] Infants born from an emergency C-section have gut microbiota that resemble the mother's skin and vaginal microbiomes.[3,8,13,33]

In the term infant, the gut is randomly colonized initially by pioneer colonizers or microbiota (Box 1) from different sites of the mother's body (eg, skin, mouth, gut, vagina, breastmilk).[28,30-32] In the first week of birth, the infant's gut is aerobic and has a neutral pH. Facultative anaerobic bacteria (growing with or without oxygen) act as pioneer colonizers (Box 1, Table 2).[28,31,32] They then reduce in number as obligate anaerobes (Table 2) begin to proliferate in the gut. As the infant grows, the pH of the gut changes. Facultative anaerobes become predominant in the gut, signaling a shift in oxygen conditions. These robust microbes are vertically transmitted (Box 1) from the mother to the child.[32] After 6 days of life, there is a transition to *Bifidobacteria* species that use human milk oligosaccharides (HMOs) as a source of carbon (Figure 2).[3,23]

In utero hypothesis. In contrast, this controversial hypothesis suggests the fetal gut microbiome is seeded during gestation when the fetus is exposed to the microbiota of the placenta or amniotic fluid. Placenta, amniotic fluid, and meconium–once considered sterile–are now being shown to be occupied by microbial communities. Preterm babies are exposed to amniotic fluid microbiota due to urinary infections (premature rupture of membranes) or chorioamnionitis (infection within the amniotic sac and the surrounding fetal membrane) during gestation.[25,34-38]

Controversies. Critics argue against the presence of microbiota in these sterile sites and suggest that laboratory contamination may be the potential source. These microbiota could also seed the neonatal gut via vertical transmission from the mother to the fetus (eg, breastmilk).[6,25,34,39]

The Second Stage: Weaning

The infant's gut microbiome undergoes a significant change during weaning when they are introduced to a solid diet.[3,23,40] The gut microbiome is compelled to mature and increase in diversity when the complexity of carbohydrate and starch components increases. There is a decrease in *Bifidobacterium* and other obligate anaerobic species. This stage of maturation sees the predominance of the phylum

Table 2. Seeding Microbes

	Facultative anaerobes	Obligate anaerobes
Term Infants	*Prevotella melaninogenica, Haemophilus parainfluenzae, Enterobacteriaceae members, Alistipes putredinis, Staphylococci, Streptococci*	*Bifidobacteria, Clostridia, Eubacteria spp, and Bacteroides*
Preterm Infants	*Staphylococcus, Enterococcus, Enterobacteraceae, Bifidobacterium*	Delayed colonization – *Bifidobacteria, Lactobacillus, and Bacteroides*

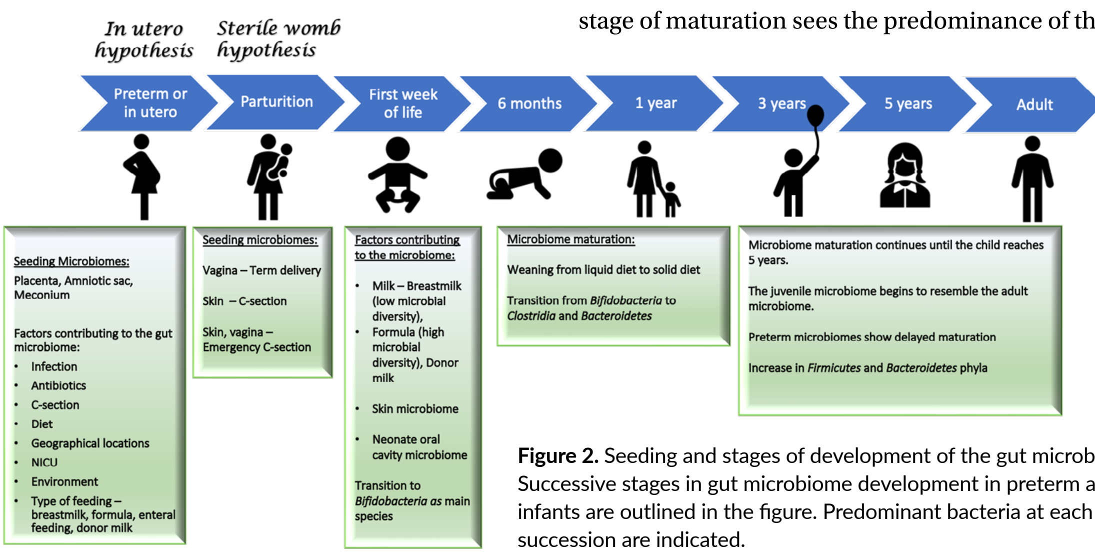

Figure 2. Seeding and stages of development of the gut microbiome. Successive stages in gut microbiome development in preterm and term infants are outlined in the figure. Predominant bacteria at each stage of succession are indicated.

Bacteriodetes and *Clostridia* species.[23,28,31,40] The gut flora is distinctly different in children aged 4 months, 12 months, 3 years, and 5 years.[3,23,29,41] As the infant grows through the first year of life, the alpha diversity (Box 1) increases when solid foods are introduced in the diet (Figure 2).[25,27,37]

The Third Stage: Stabilization of Gut Flora During Growth Into Adulthood

There is limited information on the gut microbiomes of children and adolescents. The evolution of the gut microbiome stabilizes in children after 5 years of age and appears to resemble that of adults. The 5 major phyla in an adult gut are *Firmicutes, Proteobacteria, Bacteroidetes, Actinobacteria*, and *Verrucomicrobia*. Microbial content, however, differs and is influenced by diet, geographical location, and use of antibiotics.[3,8,29,41-43] Bacterial genera of the adult gut do not resemble the genera found in children younger than 3 years.[29] With the progress to adulthood, *Bifidobacteri*a abundance reduces along with subsequent enrichment of *Firmicutes* and *Bacteroidetes* in the adult microbiome.[44]

FACTORS INFLUENCING GUT MICROBIOTA

Normal development of the gut microbiome with increasing species diversity from birth is essential to the future health of the individual.[27] Several factors enhance or impede the microbial balance in the gut.

Term Infants

In a term neonate, vaginal birth, good maternal health, breastmilk, and probiotics enhance the diversity of gut flora. Antibiotics, hospitalization, and smoking (Table 3) give rise to antimicrobial resistance genes and facilitate the growth of facultative anaerobic pathogenic bacteria.[8,13,39,45,46] The type of mother's diet, c-section birth, formula feeds, bovine-milk-fortified human milk, and the environment (eg, living with family members, daycare, pets, rural or urban lifestyle, an industrialized environment) influence gut flora maturation in different ways.[8,28,30] Gut microbiota of infants born via c-section and/or fed formula are very diverse and closely resemble mature microbiota of adults.[23] In addition, chemical factors (pH, bile acid, mucus), microbial factors (adhesion capability, metabolic pathways, bacterial enzymes), and bacteriophages influence gut microbiome diversity.[5,21]

Preterm Infants

Preterm infants show delayed development of microbial diversity and a distinct difference in species composition (Table 4) from those of age-matched term infants before 6 months.[25,37,47] Microbial colonization may occur prior to birth because of complications during gestation.[13,33,36] Gestational age plays a major role in the initial colonization and microbial diversity of the preterm infant's gut.[47] Other factors include genetics, sex, the mode of feeding (enteral; parenteral; breastfeeding), type of milk (breastmilk; formula, donor milk); pumping and storage of milk, and the environment (hospital; intensive care unit; medical interventions; antibiotics; family members).[13,27,33,37,44,45,48-51]

IMPACT OF CHANGES IN MICROBIAL DIVERSITY

Gut microbiomes of children are more susceptible to changes in diet, environment, and antibiotics than those of adults. Babies born via c-section appear to be predisposed to developing obesity and celiac disease.[8,41] Antibiotic treatment reduces microbiota diversity, leading to antibiotic-related obesity, multidrug resistance, and asthma. Gut health could be restored when treated with beneficial bacteria.[23,41] The quality of microbial diversity in the gut is

Table 3. Gut Bacteria in Term Infants

Vaginal	*Escherichia coli*, *Lactobacillus spp*, *Enterococcus Bifidobacteria (eg, Bifidobacterium breve*, *Prevotella spp*, *Bifidobacterium bifidum*, *Bifidobacterium adolecscentis*, *Bifidobacterium longum)*, *Sneathia spp*, *Streptococci*, *Atopobium vaginae* and *Gardnerella vaginalis*, *Bacteroides*, *Fecalibacteria*, *Parabacteroides*, *Lachnospiraceae*, *Ruminococcaceae*, *Christensenallaceae*, *Roseburia*, *Anaerostipes*
C-section	*Klebsiella*, *Clostridium*, *Staphylococcus*, *Haemophilus*, *Veillonella*, *Propionibacteria*, *Proteobacteria*, *Enterococcus spp*, *Corynebacterium spp*, other *Ruminococcaceae variants*, *Bifidobacterium spp*↓, *Lachnospiraceae*, *and Bacteroidaceae* species↓
Breastmilk	*Enterobacter*, *Streptococci*, *Acinetobacter*, *Staphylococci*, *Bifidobacteria*, lactic acid bacteria, *Pseudomonas*
Formula	*Clostridium difficile*, *Bacteroidetes (Bacteroides fragilis)*, *Staphylococci*, *Atopobium*, *Enterobacteria*, *Enterococci*, and *Firmicutes Lactobacilli*, *Escherichia coli*

Table 4. Gut Bacteria in Preterm Infants

C-section	*Enterococci*, *Enterobacteraceae*, *Staphylococci*, *Klebsiella*, *Mycoplasmataceae (↑ in chorioamnionitis)*, *Bacteroidetes*↓, *Escherichia*, *Bifidobacteria* ↓, *Veillonella*, *Lactobacilli* ↓, *Coprobacilli*, *Desulfovibrio*, *Carnobacteria*, *Phascolarctobacteria*, *Gammaproteobacteria*, *Firmicutes*, *Shigella*, *Clostridia* ↓, *Atopobium* ↓, *Sneathia sanguinegens*, *Fusobacterium nucleatum*
Breastmilk	*Staphylococci*, *Corynebacteria*, *Pseudomonas*, *Streptococci*, *Acinetob*
Formula	*Bifidobacteria* and *Clostridiales*
Antibiotics	*Firmicutes* and *Proteobacteria*
Hospital-associated	*Klebsiella pneumoniae*, *Yersinia*, *Enterococci*, *Serratia*, *Granulicatella*, *Proteus*, *Enterobacter aerogenes*, *Escherichia coli*
Diet-associated	*Ruminococcus bromii*, *Bacteroides vulgatus*, *Lactococci*, *Ruminococcus obeum*
Butyrate producers	*Eubacterium hallii*, *Anaerostipes caccae*, *Coprococcus eutactus*

crucial and dependent on the interplay of different factors. Despite breastfeeding, malnutrition reduces alpha diversity (increased prevalence of *Proteobacteria*) and slows down growth in children.[3,23,29,43] A Western diet of low-fiber and high-fat processed foods increases the presence of *Bacteroides* and reduces overall alpha diversity. Numerous health conditions (eg, obesity, IBD, cancer) appear to be associated with reduced alpha diversity.[23,52] In contrast, high-fiber diets increase microbial diversity and overall health in rural populations in Asia and Africa.[23,40,41,52] Geographical location appears to influence microbial diversity. People living in industrialized urban areas exhibit lower gut microbial diversity than those who live in rural areas.[42,52]

GUT MICROBIOME NETWORK

The gut microbiome does not act in isolation. Instead, microbiota or its metabolites travel to other sites of the human body and interact with their microbiomes through bidirectional or multidirectional pathways. This complex network explains the influence of the gut microbiome on our immunity, health, and even our emotions (Figure 1). Some of the gut axes are gut-liver,[24] gut-lung,[10,24,53,54] gut-brain, gut-skin, gut-liver-kidneys,[24] and gut-brain-liver.[24] Disruption to the normal functioning of these axes results in diseases such as chronic kidney disease, hepatic encephalopathy, and cardiovascular disease, nonalcoholic fatty liver disease, chronic obstructive pulmonary disease, asthma, and cystic fibrosis.[10,24,53,54] These conditions are often linked to gastrointestinal diseases. This article will focus on the gut-skin, gut-brain, and the gut-breastmilk axes.

Gut-Skin Axis

The biochemical interactions between the skin and gut microbiomes are bidirectional.[28] A dysbiotic gut microbiome may induce changes to the skin microbiome with the release of proinflammatory cytokines. This allows gut bacteria or their metabolic byproducts and toxins to enter the systemic blood circulation. The gut bacteria reach the skin and affect the integrity of the skin barrier. The resulting inflammation has been linked to chronic skin disorders (eg, psoriasis, acne, alopecia).[55,56]

Gut-Brain Axis

According to preclinical research, there are bidirectional interactions between the gut, brain, and the gut microbiome (GBM). The gut-brain axis comprises the autonomic nervous system, the gut microbiota with its metabolic products, the enteric neuroendocrine system, the hypothalamic-pituitary-adrenal system, the enteric nervous system, and the gut-associated immune system.[36,57] Research has shown that bacteria, their metabolites, and immune cells have access to the brain through the blood brain barrier (BBB).[22,58] Gut bacteria belonging to the genera *Bifidobacteria, Streptococci, Escherichia, Lactobacilli*, and *Enterococci* regulate the production of neurotransmitters (eg, GABA, serotonin, and acetylcholine), which pass through the BBB and modulate brain signaling directly or indirectly. Interactions between the nervous system and the immune system are also affected. People suffering neurological, psychiatric, and degenerative conditions (eg, depression, anxiety) also display perturbations in the diversity of their gut microbiome (eg, IBD, chronic abdominal pain).[22,57-59]

Gut-Brain-Skin Axis

The gut-brain-skin axis is gaining relevance in the consistent link between skin conditions (psoriasis, acne) and mental health (depression). The central nervous system (CNS) is regulated by neurotransmitters transmitted from the gut microbiota through the vagus nerve. Neurotransmitters facilitate the interactions between the nervous system and immune responses to skin inflammation. Mental health conditions (eg, depression) and skin conditions (eg, psoriasis) generate cytokines (eg, IL6) from the brain and the skin. This causes inflammation. Simultaneously, CNS conditions (eg, depression or anxiety) appear to cause gut dysbiosis and increase the permeability of the gut epithelial cells (leaky gut). Gut microbiota and their metabolites enter the bloodstream and trigger inflammation on the skin and in the brain.[58,60]

Human Breastmilk – Enteromammary Hypothesis

Breastmilk may play a role in seeding the infant microbiome. A quarter of the infant's gut microbiota is obtained from breastmilk, which influences its development over the individual's lifetime and protects against potential allergies.[61,62] The enteromammary hypothesis suggests that bacteria travel from the mother's gut to the lactating breast and create the breastmilk microbiome. However, this hypothesis is based on a small sample size.[51,61,63] Human breastmilk contains bioactive compounds (secretory immunoglobulin A,[64] growth factors, >200 HMOs, cytokines), immunological compounds, nutrients, and maternal gut microflora. Bioactive compounds help to develop a robust immune system in the infant.[8,44,61] As prebiotics and a source of bioactive compounds, HMOs are digested by microbiota, such as *Bifidobacteria*, in the large intestine because humans lack the enzymes to metabolize HMOs in the small intestine. HMOs (elaborate sugar complexes) are a major source of brain nourishment and prevent the growth of infectious pathogens.[8,44,61] The components of breastmilk change dynamically at each developmental stage of the infant.[65]

CONCLUSION

Despite strong associations, the vital question persists: does a health condition cause gut dysbiosis, or is the reverse true?[22,23] This topic is ripe for debate as misinformation influences public opinion. Unfortunately, it has been noted that the general population prefers to acquire information from nonmedical independent sources.[17] Popular content (eg, articles or videos) lack reliable peer-reviewed sources to support their claims on the benefits of products, such as probiotics or yogurt, on human health.[2,17] However, responsible reporting is warranted. Accurate data interpretation could influence future health policies.[1] To preserve scientific integrity, it is our responsibility as medical writers to ensure that facts and research findings on the gut microbiome are validated and appropriately disseminated. Data from large randomized clinical trials should be cautiously interpreted by assessing the relevance of statistical tests used or by distinguishing associations from cause-and-effect. When statistical data are accurately interpreted in the larger context of the human population, the significance of the results is more convincing. Although gut microbiome research is under the influence of the "health halo," we cannot deny the existence and the involvement of this extensive microbial community in human health.[2] Established as an integral part of the complex, interconnected human signaling network, the gut microbiome and its manipulation could soon form a key aspect of the diagnostic and treatment landscape.

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