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Gut Microbiota and Salivary Diagnostics: The Mouth Is Salivating to Tell Us Something

Krishna Kodukula,[1–3,*] Douglas V. Faller,[4,5] David N. Harpp,[6] Iphigenia Kanara,[7] Julie Pernokas,[8] Mark Pernokas,[8] Whitney R. Powers,[9,10] Nikolaos S. Soukos,[11] Kosta Steliou,[3,5] and Walter H. Moos[2,12,*]

Abstract

The microbiome of the human body represents a symbiosis of microbial networks spanning multiple organ systems. Bacteria predominantly represent the diversity of human microbiota, but not to be forgotten are fungi, viruses, and protists. Mounting evidence points to the fact that the "microbial signature" is host-specific and relatively stable over time. As our understanding of the human microbiome and its relationship to the health of the host increases, it is becoming clear that many and perhaps most chronic conditions have a microbial involvement. The oral and gastrointestinal tract microbiome constitutes the bulk of the overall human microbial load, and thus presents unique opportunities for advancing human health prognosis, diagnosis, and therapy development. This review is an attempt to catalog a broad diversity of recent evidence and focus it toward opportunities for prevention and treatment of debilitating illnesses.

Keywords: biofilm; dental; medicinal food; microbiota; oral; salivary

Introduction

The interconnected network of microorganisms (bacteria, viruses, fungi, and protists) that live in and on our body take up residence mainly in the oral and nasal cavities (oral microbiota), on the skin (skin microbiota), in the gastrointestinal (GI) tract (gut microbiota), and in females, in the genital tract (mostly as vaginal microbiota) (Fig. 1).[1–8] Mounting data show that for each individual, the collective composition of their microbiota (microbiome)[3,9,10] is host-specific and relatively stable over time.[4,11–13]

Of the different ecosystems of flora that inhabit the human body, the gut microbiota system is emerging as the preeminent "microbial organ" of study, and there is great expectation that by better understanding the complexity of the role of microbiota, our microbiome will become an indispensable and integral part of our personalized healthcare in preventing and/or treating diseases more effectively and in a more precise and targeted clinical approach.[3,14–19] Indeed, gaining a better understanding of the gut microbiota system may help to enable a revolution in precision medicine[20,21]

[1]Bridgewater College, Bridgewater, Virginia.
[2]ShangPharma Innovation, Inc., South San Francisco, California.
[3]PhenoMatriX, Inc., Natick, Massachusetts.
[4]Department of Medicine, Boston University School of Medicine, Boston, Massachusetts.
[5]Cancer Research Center, Boston University School of Medicine, Boston, Massachusetts.
[6]Department of Chemistry, McGill University, Montreal, Canada.
[7]Consulate General of Greece in Boston, Boston, Massachusetts.
[8]Advanced Dental Associates of New England, Woburn, Massachusetts.
[9]Department of Health Sciences, Boston University, Boston, Massachusetts.
[10]Department of Anatomy, Boston University School of Medicine, Boston, Massachusetts.
[11]Dana Research Center, Department of Physics, Northeastern University, Boston, Massachusetts.
[12]Department of Pharmaceutical Chemistry, School of Pharmacy, University of California San Francisco, San Francisco, California.

*Address correspondence to: Walter H. Moos, PhD, Department of Pharmaceutical Chemistry, School of Pharmacy, University of California San Francisco, UCSF Box 2280, 600 16th Street, Genentech Hall S512D, San Francisco, CA 94143, E-mail: walter.moos@ucsf.edu or Krishna Kodukula, PhD, Bridgewater College, 402 East College Street, Bridgewater, VA 22812, E-mail: kkodukula@gmail.com
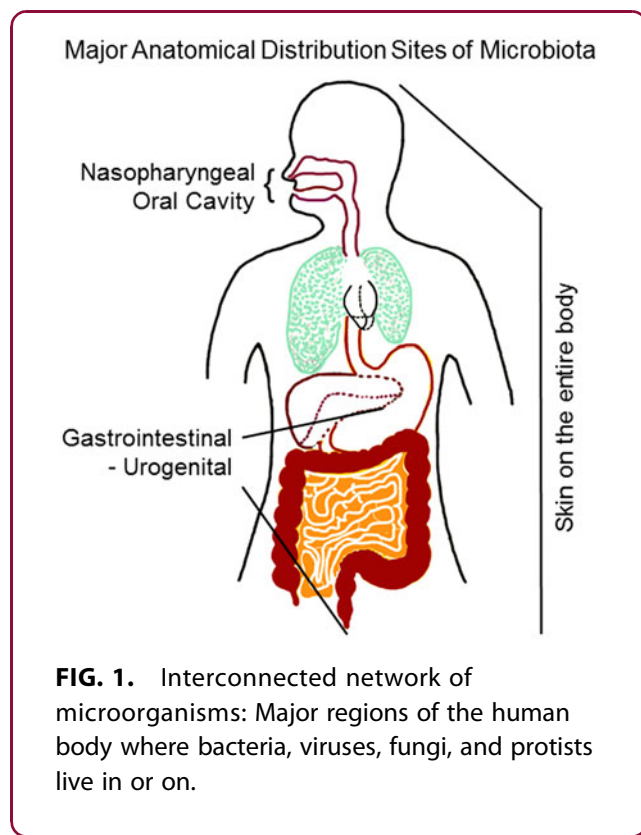
FIG. 1. Interconnected network of microorganisms: Major regions of the human body where bacteria, viruses, fungi, and protists live in or on.

Table 1. Symbiotic Host–Flora Relationship: Examples of Important Roles That Gut Microbes Play in Functions Essential to Human Health and Survival

Function	Effect
Chemical transformation and metabolism of xenobiotics	Eliminate or transform environmental chemicals in the air we breathe, extraneous food additives, pharmaceuticals
Immune system	Induction, basic development, training and function
Production of SCFAs	Inhibit inflammation; influence multiple regulatory pathways (thereby affecting epigenetic regulation of gene expression)

SCFA, short-chain fatty acid.

Consequently, it should not be surprising that gut dysbiosis (also called dysbacteriosis or gut microbial imbalance or maladaptation) can profoundly affect our wellbeing,[42] lead to the manifestation of neuropsychiatric symptoms and conditions,[43–46] and underlie a multitude of immune-related disorders (gut–brain-immune axis).[47–50] Gut dysbiosis may also exacerbate the progression of a number of common and often chronic diseases. Allergies, atherosclerosis, colorectal cancer, diabetes, inflammatory bowel disease, neurological conditions, and obesity are some examples.[50–54]

An association between aberrant mental states and digestive disturbances was described by Hippocrates[55] and is the single consistently linked comorbidity reported in the medical literature from ancient times to the present.[56] Diet figures prominently in maintaining or altering the commensal homeostasis composition of the GI microbiota,[10,14,54,57–59] and the formulation of diets rich in functional medicinal foods (food-drugs)[60] is driving the emergent field of (neuro)regenerative nutrition.[61,62] Although the mechanistic pathways remain mostly obscure, numerous studies show that through reciprocal interactions with the gut–brain axis[51,63–67] the gut microbiome can influence neural development, cognition, and behavior.[43,46,54,68–70] In turn, changes in behavior can alter the gut microbial composition.[43,67,71,72] Consuming the Mediterranean diet in particular has been demonstrated to improve the health of patients with various chronic diseases[26,73–78] (presumably by altering the gut microbiome)[26,79–83] and can help mitigate with some degree of efficacy abnormal behavior associated with neuropsychiatric conditions.[68] Thus, opting to incorporate a tailor-made diet plan in the overall treatment of neurologic conditions, including autism and schizophrenia, is increasingly common practice.[10,41,68,71,72,84–86] However, for microbiota to

across a wide range of diagnostic, preventive, and therapeutic approaches.[15,17]

Of the 100 trillion or so microorganisms that make up the human microbiome (accounting for 1–3% of a person's body weight),[22,23] approximately half (1–2 kg) reside in the GI tract, which hosts the largest and most diverse collection.[22,24] A symbiotic host–flora relationship[25,26] has evolved between them and us, and as a result, we are dependent on our gut microbes to perform many functions that are essential to our health and survival. They chemically transform and metabolize xenobiotics, which we take willingly (e.g., pharmaceuticals) and/or unwillingly (e.g., environmental chemicals in the air we breathe and extraneous additives in our foods),[27–29] they play a fundamental role in the induction, basic development, training, and function of our immune system,[26,30–33] and in the process of helping us digest fibrous foods, they produce short-chain fatty acids[25,26,34] that inhibit inflammation[35–37] and affect epigenetic regulation of gene expression by influencing multiple regulatory mechanisms (Table 1). Importantly, these regulatory mechanisms include acetylation of DNA-associated histone proteins and methylation of DNA.[10,33,38–41]

play a clinical role in nutritional interventions for maintaining (brain) health,[68,87] a reliable diagnostic determination of the gut microbial composition is wanting[88–91]—hence, the focus of this forward-looking review article.

Fecal-Derived Microbiota

The majority (∼60%) of the bacterial species residing in the GI tract (primarily the stomach, small intestine, and large intestine)[92] are reported to be unculturable.[93] In addition, gut microbiota are not readily accessed,[52] and characterization of intestinal microbiota currently relies on analysis of the microbial composition in patient-derived fecal (stool) samples,[94,95] using DNA-based culture-independent methods as a surrogate representation.[71,93,94,96,97] However, the method of sample collection, laboratory handling, analysis, bioinformatic processing of the data, and other factors can greatly affect microbiome study findings.[93,98–100] When a healthy state of the gut microbiota is altered, opportunistic bacteria such as *Clostridium difficile* (sometimes referred to as *C. diff.*) can grow and cause an infection that is difficult to treat.[101,102] Orally administered capsules containing an ecology of bacteria in spore form enriched from stool donations obtained from healthy, screened donors[103,104] are being used in an increasing number of clinical trials (www.clinicaltrials.gov). The hope is that such bacterial preparations will be successful in treating various conditions, including *C. difficile* infection.[103,105,106] The composition of fecal microbiota as a valid surrogate representation of the eubiotic (normal) gut microbiome system aimed to be reconstituted[71,103,104,107,108] is also gaining greater scrutiny,[104,109] particularly if antibiotics were taken within 12 months before stool collection.[98] Indeed, because of resulting alterations in a patient's microbiome, the impact of antibiotics on the life-saving potential of powerful new therapeutic approaches, including immuno-oncology checkpoint inhibitors and other state-of-the-art immune system modulators, is currently a hot topic in medical practice.[110,111]

Oral Cavity-Derived Microbiota

There is mounting evidence that the spectrum of microbial species living in the mouth is, both in diversity and in composition, a close representation of the microbiota inhabiting the upper GI tract. In a study to evaluate the influence of proton pump inhibitors on the luminal microbiota in the GI tract reported by Tsuda et al.,[112] an analysis of microbial samples taken from the oral cavity (saliva), the stomach (gastric fluid), and the colon (stools) of 45 individuals found that the bacteria are similar in overall species richness among the three microbiota irrespective of their different habitats (Fig. 2). Importantly, however, the bacterial composition of the fecal microbiota was shown to be different from those of salivary and gastric fluid microbiota.[112] Furthermore, the interindividual variability of fecal microbiota was much higher compared with that of salivary and gastric fluid microbiota as might be expected with the colon habitat being completely different from the other two habitats with respect to their biological and ecological features.[112] Curiously, in a seemingly unconnected relationship, the placental microbiome[8] is also reported to share similarity with that of the oral cavity and not those of the more proximal vaginal or gut flora.[113–116]

Rapid advances in genome sequencing technologies have given rise to user-friendly commercially available kits with buccal swabs for collecting genomic material.[118] (It is worth noting the current lack of standards, accessible control data, and variable results from one commercial provider to another; nonetheless, our expectation is that standardization and suitable comparisons of data and results would quickly follow once the practice is adopted and dentists are more fully engaged.) Located at the entrance of the digestive apparatus feeding into the GI tract, the mouth (oral cavity) also provides a convenient, accessible site for swabbing microbial samples.[118–121] The surfaces of teeth, however, accumulate distinct biofilms (Fig. 3) in comparison to mucosal surfaces in the oral cavity,[120,122,123] and some species of microbes from dental biofilms may not be well represented in saliva alone, particularly dental caries-causing bacteria.[124,125] Nonetheless, a growing body of evidence suggests that alterations in the oral microbiome have potential in sentinel diagnostic and prognostic applications.[102,110,118,120–122,125–129]

The healthy human mouth hosts a complex and durable ecosystem of hundreds of different species of microbes that are largely living on the surfaces of teeth as dental biofilms.[122,130,131] When microbial homeostasis in the oral cavity is perturbed (as with excessive and frequent consumption of sugar), opportunistic pathogens can selectively grow to dominate dental biofilms (dysbiosis) and predispose the oral cavity to inflammation, infection, and tooth decay.[132,133] Although rare, there are reported cases in which a life-threatening bacterial infection from a tooth abscess has spread intracranially to the brain.[134] Better precedent is the apparent link between
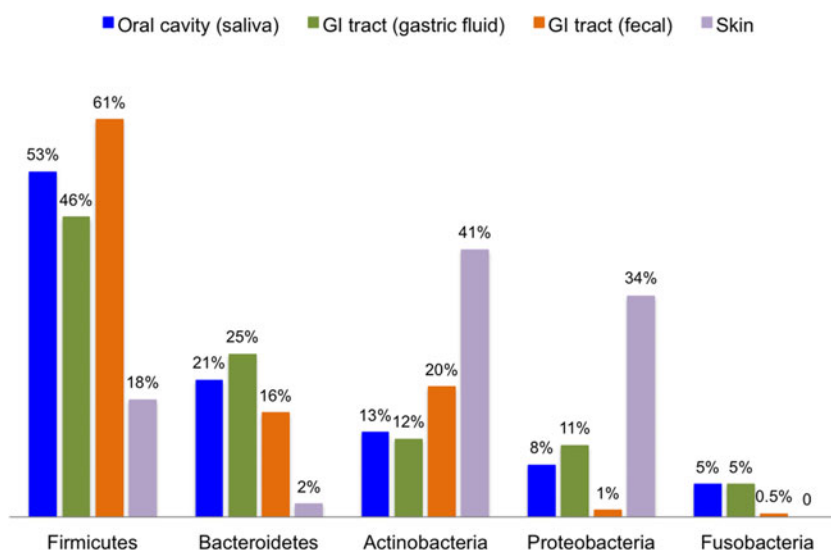
FIG. 2. Relative Composition (%) of the major phyla of bacteria found in microbiota samples. Data for Oral cavity, GI tract (gastric fluid), and GI tract (fecal) were from Tsuda et al.[112] Skin microbiota composition was obtained from van Rensburg et al.[117] Genital tract (vagina) information, from Miles et al.,[8] is highly variable (Firmicutes > Proteobacteria > Bacteroidetes > Actinobacteria >> other) and is not plotted. GI, gastrointestinal.

periodontal health and cardiovascular disease.[135–137] Undeniably, antibiotics tend to be overused,[138,139] and because antibiotics kill microbes indiscriminately, their misuse in treating infections due to viruses and not bacteria[140] is a leading cause of antibiotic resistance. During antibiotic therapy, unlike the oral and upper gut microbiomes that resist induced perturbation of their eubiotic state, the microbiota in the colon habitat are vulnerable,[98,112] and recent exposure to antibiotics is an exclusionary criterion in screening donors for fecal microbiota transplantation.[104]

An evolving alternative to antibiotics for selectively killing odor-causing bacteria in the mouth, including pathogenic bacteria that could seed growth in the gut, is a technique that exposes the oral cavity to blue light for a short period of time.[141–144] The bacterial compositions in the human oral and gut microbiomes are closely related to each other.[112] Interestingly, a corroborative analogy from the agricultural sector comes into play here. The oral microbiomes of dairy cattle are also similar in constitution with respect to their individual gut microbiomes, and oral samples are routinely taken as
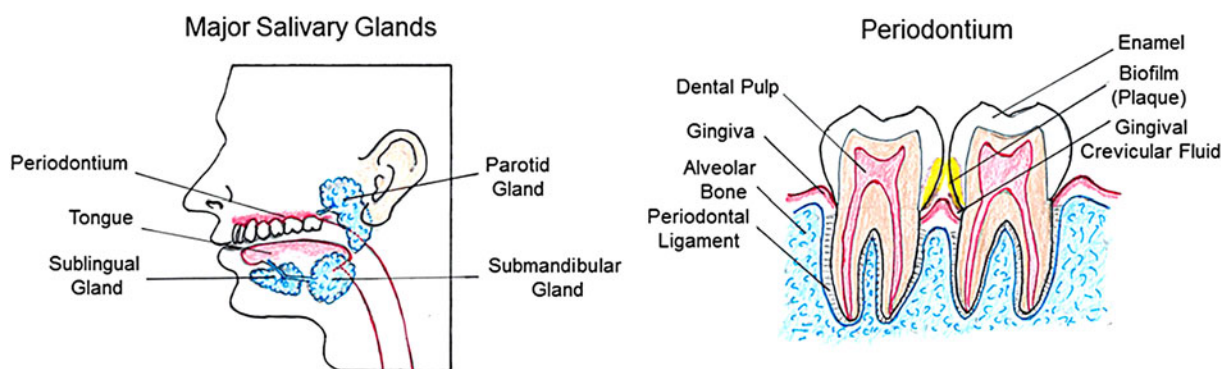

FIG. 3. The major salivary glands and the periodontium.

noninvasive proxies for assessing the health and potential pathogenic growth of bacteria in the microbial community of their rumen.[145] Another major contributor to antibiotic resistance is the widespread use of antibiotics in animal feed[146]—prompting a legislated ban of all food animal growth-promoting antibiotics in Sweden that has been in effect since 1986. A little more than a decade later the European Union also banned such antibiotic use as a "Precautionary Principle."[147] However, the total withdrawal of this class of antibiotics is now associated with a deterioration in animal health, including increased diarrhea, weight loss, and mortality due to *Escherichia coli* and *Lawsonia intracellularis* in early postweaning pigs and clostridial necrotic enteritis in broilers.[147] To compensate, in the hope of providing a means for reducing the superfluous use of such drugs in our food-production chain in general, agricultural businesses are investigating oral exposure to blue light as a potential replacement for classical antibiotic prophylaxis in food animals.[148,149]

Leveraging the Oral Microbiome in Diagnosing and Treating Disease

Although the oral cavity is continuously subjected to a barrage of host and environmental insults, the oral microbiome remains relatively stable over time in healthy people.[122,131,150,151] Given this fact, changes in the profile of the oral microbiome may provide correlative insight into the onset, progression, and recurrence of disease.[102,118,120–122,125–129,152] For example, in a retrospective clinical assessment, Zawadzki et al.[152] examined the oral environment in different human populations and compared and determined the pathogenicity of the resident oral microbiota linked to health complications in three distinct patient groups. A total of 95 patients who required dental or surgical interventions were evaluated for oral cavity microbiota risk factors associated with general or local infections. This included individuals with masticatory system malformations (30 patients), recipients of kidney allografts (30 patients), and a control group of subjects without surgical needs (35 patients) treated conservatively. Using standard microscopy and *in vitro* culture techniques, differences were noted in bacterial strains between the patient groups requiring surgical treatment and the generally healthy subjects from the control group. The results of this study strongly support the notion that preventive oral cavity microbiota assessment should be performed on patients requiring oral surgery because they are at risk of pathogenic bacterial

colonization and infections that have the potential to spread. In general, an examination of the oral cavity environment for infectious microbiota could help reduce surgical complications and also support and/or guide the surgical treatment.

Additional evidence reinforcing similarities between the oral and gut microbiomes is observed in their reciprocal exchange of bacterial pathogens. Diabetes is a systemic chronic illness intimately associated with periodontal disease.[131,133,153] Dysbiosis of the oral microbiome can lead to periodontitis,[136,153] which promotes pathogenic bacterial growth and facilitates dissemination of oral bacteria systemically.[131,153] A causative link between oral pathogens and changes in the composition of the gut microbiota as well as inflammatory changes in various tissues and organs has been demonstrated in mice.[154–157] Conversely, emerging evidence shows that diabetes, a chronic disease linked to alterations in the gut microbiome,[18,50,52,54,102,158,159] causes a pathogenic shift in the oral microbiome with increased bone loss and inflammation in the mouth that ultimately give way to periodontal disease.[160] Suppressing the growth of opportunistic pathogens in the oral cavity is important in reducing the systemic dissemination of oral bacteria and crucial in the daily practice of good oral hygiene, especially in the management of diabetes.[131,153] Oral photo-inactivation is a promising nonobtrusive and nonantibiotic method that may have advantage in this effort.[144,149,161]

While inconclusive and speculative, there are sporadic reports in the literature that imply the chronic oral infection of periodontitis may be a risk factor for Alzheimer's disease (AD) and Parkinson's disease (PD).[162–164] Elevated antibodies to periodontal disease bacteria in subjects were observed years before the onset of symptoms in people suffering from AD,[164,165] inferring that there was an increased translocation of bacteria and/or bacterial toxins from the mouth into the bloodstream.[162] An investigative study by Pereira et al.[163] identified differences in beta diversity (which quantifies community composition similarity between samples) and abundances of individual bacterial taxa in oral microbiota of PD patients and control subjects. However, an increase in the abundance of opportunistic oral pathogens was detected in males, both with and without PD. Nonetheless, the measured differences argue for further exploration of oral microbiota as a possible biomarker for PD.[163]

Rheumatoid arthritis (RA) is an inflammatory autoimmune disease strongly associated with periodontal disease.[166] In a study by Zhang et al.,[167] dysbiosis was

evident in the gut and oral microbiomes of RA patients, and there was a concordance between the two microbiomes. Differences in the gut and/or oral microbiomes distinguished individuals with RA from healthy controls and were used to stratify individuals according to their response to therapy.[167] The altered composition of the gut or oral microbiomes in individuals with RA correlated with the prognosis and diagnosis of the disease.[167] Moreover, in two separate and unrelated double-blind randomized placebo-controlled clinical trials[168,169] aimed to evaluate the benefit of oral probiotic supplements as an adjunct microbial therapeutic intervention, the RA patients who received daily capsules of the probiotic *Lactobacillus casei* 01 over a 2-month period had statistically significant improvements in their disease activity and inflammatory status compared with controls.[166,168,169]

Concluding Remarks

Obesity is an expanding healthcare issue worldwide[170,171] and is a leading risk factor to a plethora of chronic conditions and diseases associated with dysbiosis in the oral and gut microbiomes—cardiovascular, cancer, diabetes, periodontitis, and RA are principal examples.[18,50,59,172] Although the science exposing how the human microbiome influences the development and maintenance of the human body is still in the embryonic stage, the existing data show unequivocally that microbiota and our wellbeing are intimately linked. As noted in this review, the gut microbiome is the preeminent microbial organ of study for association, diagnosis, prognosis, and treatment of disease. Sampling the gut microbiota requires intervention for direct access. The oral cavity microbiome is proving to be a relevant surrogate representation of gut microbiota. The mouth is a psychologically more palatable and more easily accessed body site for microbial sampling by the patient as well as by the healthcare professional. With the ever increasing pressure to lower healthcare costs, prevention of disease has the greatest impact. Saliva and mucosal swabbing, including sampling of dental biofilms, could be made part of the routine dental exam. This scenario is likely to become common practice in preventive medicine, if not more so than giving a blood-sample.[173] Furthermore, capitalizing on the growing insights in this field, both new therapies and novel ways to make old therapies more effective are likely to emerge. The human microbiome may even find itself at the very center of the future of medicine—precision, personalized, and ever safer and more efficacious.[4] The food industry is already shifting toward developing microbiota-directed foods[174] and the U.S. Food and Drug Administration is considering classifying these altered foods as medical foods that may need to be regulated.[174,175]

In closing, we note that the cosmetic industry has begun to explore the relationship between the human microbiome and healthy skin to help correct skin microbe imbalances that are believed to play an underlying role in skin conditions such as acne and eczema as well as more minor maladies such as dryness and wrinkles.[23] Moreover, diabetic retinopathy, age-related macular degeneration, glaucoma, and cataracts are eye diseases that cause visual impairment and ultimately blindness, affecting millions of people worldwide.[176] The eye is an immunologically privileged site, and dysregulation of the endogenous microbiota can have profound effects on host immune function.[177] The surface of the eye is believed to harbor its own unique and immunoprotective commensal ecosystem (ocular microbiome), and it has barely begun to be explored.[178–180]

Although the encompassing mechanisms and pathways are not fully recognized or elucidated, and there is much work yet to be done as we apply our growing understanding of the human microbiome, microbiome medicine (the potential of the microbiome in treatment and diagnosis) clearly has clinical implications that no longer can be ignored.[17,181,182]

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Authors' Contributions

All authors contributed to the writing of this article and agreed to its final content.

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Abbreviations Used

AD = Alzheimer's disease
GI = gastrointestinal
PD = Parkinson's disease
RA = rheumatoid arthritis
SCFA = short-chain fatty acid