COMPREHENSIVE REVIEW

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

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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}

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Major Anatomical Distribution Sites of Microbiota

FIG. 1. Interconnected network of microorganisms: Major regions of the human body where bacteria, viruses, fungi, and protists live in or on.

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}

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 Hippocrates⁵⁵ 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

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 microbiome⁸ 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 bacteria¹⁴⁰ 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 feed¹⁴⁶—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 foods¹⁷⁴ 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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References

1. Blekhman R, Goodrich JK, Huang K, et al. Host genetic variation impacts microbiome composition across human body sites. *Genome Biol.* 2015;16:191.

2. Franasia JM, Scott RT. Reproductive tract microbiome in assisted reproductive technologies. *Fertil Steril*. 2015;104:1364–1371.
3. Marchesi JR, Adams DH, Fava F, et al. The gut microbiota and host health: a new clinical frontier. *Gut*. 2016;65:330–339.
4. Blum HE. The human microbiome. *Adv Med Sci*. 2017;62:414–420.
5. Carding SR, Davis N, Hoyle L. Review article: the human intestinal virome in health and disease. *Aliment Pharmacol Ther*. 2017;46:800–815.
6. Garg N, Luzzatto-Knaan T, Melnik AV, et al. Natural products as mediators of disease. *Nat Prod Rep*. 2017;34:194–219.
7. Limon JJ, Skalski JH, Underhill DM. Commensal fungi in health and disease. *Cell Host Microbe*. 2017;22:156–165.
8. Miles SM, Hardy BL, Merrell DS. Investigation of the microbiota of the reproductive tract in women undergoing a total hysterectomy and bilateral salpingo-oophorectomy. *Fertil Steril*. 2017;107:813–820.
9. Lederberg J, McCray AT. 'Ome sweet' omics—A genealogical treasury of words. *Scientist*. 2001;15:8.
10. Moos WH, Faller DV, Harpp DN, et al. Microbiota and neurological disorders: a gut feeling. *BioRes Open Access*. 2016;5:137–145.
11. Zoetendal EG, Akkermans AD, De Vos WM. Temperature gradient gel electrophoresis analysis of 16S rRNA from human fecal samples reveals stable and host-specific communities of active bacteria. *Appl Environ Microbiol*. 1998;64:3854–3859.
12. Faith JJ, Guruge JL, Charbonneau M, et al. The long-term stability of the human gut microbiota. *Science*. 2013;341:1237439.
13. Fond G, Boukouaci W, Chevalier G, et al. The “psychomicrobiotic”: targeting microbiota in major psychiatric disorders: a systematic review. *Pathol Biol*. 2015;63:35–42.
14. Zmora N, Zeevi D, Korem T, et al. Taking it personally: personalized utilization of the human microbiome in health and disease. *Cell Host Microbe*. 2016;19:12–20.
15. Chuong KH, Mack DR, Stintzi A, et al. Human microbiome and learning healthcare systems: integrating research and precision medicine for inflammatory bowel disease. *OMICS*. 2017 [Epub ahead of print]; DOI:10.1089/omi.2016.0185.
16. Donovan SM. Introduction to the special focus issue on the impact of diet on gut microbiota composition and function and future opportunities for nutritional modulation of the gut microbiome to improve human health. *Gut Microbes*. 2017;8:75–81.
17. Kuntz TM, Gilbert JA. Introducing the microbiome into precision medicine. *Trends Pharmacol Sci*. 2017;38:81–91.
18. Vaiserman AM, Koliada AK, Marotta F. Gut microbiota: a player in aging and a target for anti-aging intervention. *Ageing Res Rev*. 2017;35:36–45.
19. Zhang G, Heng HH. Human microbiome and environmental disease. *Environ Dis*. 2017;2:5–8.
20. Ashley EA. The precision medicine initiative. *JAMA*. 2015;313:2119–2120.
21. Collins FS, Varmus H. A new initiative on precision medicine. *N Engl J Med*. 2015;372:793–795.
22. Forsythe P, Kunze WA. Voices from within: gut microbes and the CNS. *Cell Mol Life Sci*. 2013;70:55–69.
23. Reisch MS. Cosmetics: the next microbiome frontier. *Chem Eng News*. 2017;95:30–34.
24. Mangiola F, Ianiro G, Franceschi F, et al. Gut microbiota in autism and mood disorders. *World J Gastroenterol*. 2016;22:361–368.
25. Oleskin AV, Shenderov BA. Neuromodulatory effects and targets of the SCFAs and gasotransmitters produced by the human symbiotic microbiota. *Microb Ecol Health Dis*. 2016;27:30971.
26. Rook G, Bäckhed F, Levin BR, et al. Evolution, human-microbe interactions, and life history plasticity. *Lancet*. 2017;390:521–530.
27. Claus SP, Guillou H, Ellero-Simatos S. The gut microbiota: a major player in the toxicity of environmental pollutants? *Nat Biofilms Microb*. 2016;2:16003.
28. Enright EF, Gahan CGM, Joyce SA, et al. The impact of the gut microbiota on drug metabolism and clinical outcome. *Yale J Biol Med*. 2016;89:375–382.
29. Koppel N, Rekdal VM, Balskus EP. Chemical transformation of xenobiotics by the human gut microbiota. *Science*. 2017;356:eaag2770.
30. Belkaid Y, Hand TW. Role of the microbiota in immunity and inflammation. *Cell*. 2014;157:121–141.
31. Estes ML, McAllister AK. Immune mediators in the brain and peripheral tissues in autism spectrum disorder. *Nat Rev Neurosci*. 2015;16:469–486.
32. Grogan D. The microbes within. *Nature*. 2015;518:52.
33. Moos WH, Pinkert CA, Irwin MH, et al. Epigenetic treatment of persistent viral infections. *Drug Dev Res*. 2017;78:24–36.
34. Darshi M, Van Espen B, Sharma K. Metabolomics in diabetic kidney disease: unraveling the biochemistry of a silent killer. *Am J Nephrol*. 2016;44:92–103.
35. Huang W, Guo H-L, Deng X, et al. Short-chain fatty acids inhibit oxidative stress and inflammation in mesangial cells induced by high glucose and lipopolysaccharide. *Exp Clin Endocrinol Diabetes*. 2017;125:98–105.
36. López RL, Burgos MJG, Gálvez A, et al. The human gastrointestinal tract and oral microbiota in inflammatory bowel disease: a state of the science review. *APMIS*. 2017;125:3–10.
37. van der Beek CM, Dejong CHC, Troost FJ, et al. Role of short-chain fatty acids in colonic inflammation, carcinogenesis, and mucosal protection and healing. *Nutr Rev*. 2017;75:286–305.
38. Steliou K, Boosalis MS, Perrine SP, et al. Butyrate histone deacetylase inhibitors. *BioRes Open Access*. 2012;1:192–198.
39. Irwin MH, Moos WH, Faller DV, et al. Epigenetic treatment of neurodegenerative disorders: Alzheimer and Parkinson diseases. *Drug Dev Res*. 2016;77:109–123.
40. Krautkramer KA, Kreznar JH, Romano KA, et al. Diet-microbiota interactions mediate global epigenetic programming in multiple host tissues. *Mol Cell*. 2016;64:1–11.
41. Moos WH, Maneta E, Pinkert CA, et al. Epigenetic treatment of neuropsychiatric disorders: autism and schizophrenia. *Drug Dev Res*. 2016;77:53–72.
42. Karkman A, Lehtimäki J, Ruokolainen L. The ecology of human microbiota: dynamics and diversity in health and disease. *Ann NY Acad Sci*. 2017;1399:78–92.
43. Rogers GB, Keating DJ, Young RL, et al. From gut dysbiosis to altered brain function and mental illness: mechanisms and pathways. *Nat Mol Psychiatry*. 2016;21:738–748.
44. Sampson TR, Debelius JW, Thron T, et al. Gut microbiota regulate motor deficits and neuroinflammation in a model of Parkinson's disease. *Cell*. 2016;167:1469–1480.
45. Zheng P, Cheng K, Zeng L, et al. A new pathway for the gut microbiota to modulate the brain: activation of pattern-recognition receptors by microbial products. *Nat Mol Psychiatry*. 2016;22:162–163.
46. Arentsen T, Qian Y, Gkotzsis S, et al. The bacterial peptidoglycan-sensing molecule Pglrp2 modulates brain development and behavior. *Nat Mol Psychiatry*. 2017;22:257–266.
47. Stolzenberg E, Berry D, Yang D, et al. A role for neuronal alpha-synuclein in gastrointestinal immunity. *J Innate Immun*. 2017;9:456–463.
48. Wadman M. The rogue protein behind Parkinson's disease may also protect your gut. *Science*. 2017; doi:10.1126/science.aan7025.
49. Levy M, Kolodziejczyk AA, Thaïs CA, et al. Dysbiosis and the immune system. *Nat Rev Immunol*. 2017;17:219–232.
50. Postler TS, Ghosh S. Understanding the holobiont: how microbial metabolites affect human health and shape the immune system. *Cell Metabol*. 2017;26:110–130.
51. Dinan TG, Cryan JF. The microbiome-gut-brain axis in health and disease. *Gastroenterol Clin N Am*. 2017;46:77–89.
52. Eain MMG, Baginska J, Greenhalgh K, et al. Engineering solutions for representative models of the gastrointestinal human-microbe interface. *Engineering*. 2017;3:60–65.
53. Mittal R, Debs LH, Patel AP, et al. Neurotransmitters: the critical modulators regulating gut-brain axis. *J Cell Physiol*. 2017;232:2359–2372.
54. Proctor C, Thiennimitr P, Chattipakorn N, et al. Diet, gut microbiota and cognition. *Metab Brain Dis*. 2017;32:1–17.
55. Hippocrates. ~460-380 BCE. On ancient medicine. In: *The works of Hippocrates*. Translated by Dunkas N, Sioras N. (eds.) Diachronic Publications: Athens, Hellas, 1998, pp. 81–170.
56. Severance EG, Prandovszky E, Castiglione J, et al. Gastroenterology issues in schizophrenia: why the gut matters. *Curr Psychiatry Rep*. 2015;17:27.
57. Kashtanova DA, Popenko AS, Tkacheva ON, et al. Association between the gut microbiota and diet: fetal life, early childhood, and further life. *Nutrition*. 2016;32:620–627.
58. Rowland I, Gibson G, Heinken A, et al. Gut microbiota functions: metabolism of nutrients and other food components. *Eur J Nutr*. 2017 [Epub ahead of print]; DOI:10.1007/s00394-017-1445-8.
59. Selber-Hnativ S, Rukundo B, Ahmadi M, et al. Human gut microbiota: toward an ecology of disease. *Front Microbiol*. 2017;8:1265.

60. Pallister T, Spector TD. Food: a new form of personalised (gut microbiome) medicine for chronic diseases? *J Royal Soc Med*. 2016;109:331–336.
61. Mariño E, Richards JL, McLeod KH, et al. Gut microbial metabolites limit the frequency of autoimmune T cells and protect against type 1 diabetes. *Nat Immunol*. 2017;18:552–562.
62. Steindler DA, Reynolds BA. Perspective: neuroregenerative nutrition. *Adv Nutr*. 2017;8:546–557.
63. Oleskin AV, El-Registan GI, Shenderov BA. Role of neuromediators in the functioning of the human microbiota: “Business talks” among microorganisms and the microbiota-host dialogue. *Microbiology*. 2016;85:1–22.
64. Bellono NW, Bayrer JR, Leitch DB, et al. Enterochromaffin cells are gut chemosensors that couple to sensory neural pathways. *Cell*. 2017;170:185–198.
65. Dinan TG, Cryan JF. Gut–brain axis in 2016: brain–gut–microbiota axis—mood, metabolism and behavior. *Nat Rev Gastroenterol Hepatol*. 2017;14:69–70.
66. Mudd AT, Berding K, Wang M, et al. Serum cortisol mediates the relationship between fecal *Ruminococcus* and brain N-acetylaspartate in the young pig. *Gut Microbes*. 2017 [Epub ahead of print]; DOI:10.1080/19490976.2017.1353849.
67. Tillisch K, Mayer E, Gupta A, et al. Brain structure and response to emotional stimuli as related to gut microbial profiles in healthy women. *Psychosom Med*. 2017;79:905–913.
68. Sandhu KV, Sherwin E, Schellekens H, et al. Feeding the microbiota-gut-brain axis: diet, microbiome, and neuropsychiatry. *Transl Res*. 2017;179:223–244.
69. Sharon G, Sampson TR, Geschwind DH, et al. The central nervous system and the gut microbiome. *Cell*. 2017;167:915–932.
70. van de Wouw M, Schellekens H, Dinan TG, et al. Microbiota-gut-brain axis: modulator of host metabolism and appetite. *J Nutr*. 2017;147:727–745.
71. Li Q, Han Y, Dy ABC, et al. The gut microbiota and autism spectrum disorders. *Front Cell Neurosci*. 2017;11:120.
72. Schwarz E, Maukonen J, Hyttiäinen T, et al. Analysis of microbiota in first episode psychosis identifies preliminary associations with symptom severity and treatment response. *Schizophrenia Res*. 2017 [Epub ahead of print]; DOI:10.1016/j.schres.2017.04.017.
73. Del Chierico F, Vernocchi P, Dallapiccola B, et al. Mediterranean diet and health: food effects on gut microbiota and disease control. *Int J Mol Sci*. 2014;15:11678–11699.
74. Yang J, Farioli A, Korre M, et al. Dietary preferences and nutritional information needs among career firefighters in the United States. *Glob Adv Health Med*. 2015;4:16–23.
75. Prieto MS, Kales SN. Dietary, lifestyle behaviors and obesity: towards modern science. *J Obes Eat Disord*. 2016;2:2.
76. Ayuso MI, Gonzalo-Gobernado R, Montaner J. Neuroprotective diets for stroke. *Neurochem Int*. 2017;107:4–10.
77. Della Corte C, Mosca A, Vania A, et al. Good adherence to the Mediterranean diet reduces the risk for NASH and diabetes in pediatric patients with obesity: the results of an Italian study. *Nutrition*. 2017;39–40:8–14.
78. Sotos-Prieto M, Bhupathiraju SN, Mattei J, et al. Association of changes in diet quality with total and cause-specific mortality. *N Engl J Med*. 2017;377:143–153.
79. Rampelli S, Candela M, Turrone S, et al. Microbiota and lifestyle interactions through the lifespan. *Trends Food Sci Technol*. 2016;57:265–272.
80. Buford TW. (Dis)trust your gut: the gut microbiome in age-related inflammation, health, and disease. *Microbiome*. 2017;5:80.
81. Mitsou EK, Kakali A, Antonopoulou S, et al. Adherence to the Mediterranean diet is associated with the gut microbiota pattern and gastrointestinal characteristics in an adult population. *Br J Nutr*. 2017;117:1645–1655.
82. Salas-Salvadó J, Guasch-Ferré M, Díaz-López A, et al. Yogurt and diabetes: overview of recent observational studies. *J Nutr*. 2017;147:1452S–1461S.
83. Tremblay A, Panahi S. Yogurt consumption as a signature of a healthy diet and lifestyle. *J Nutr*. 2017;147:1476S–1480S.
84. Bonvicini F, Simeoni F, Gasbarrini G, et al. Wheat—a precious nutrient that can become harmful: wheat/gluten related disorders. *J Clin Gastroenterol Hepatol*. 2017;1:2.
85. Ding HT, Taur Y, Walkup JT. Gut microbiota and autism: key concepts and findings. *J Autism Dev Disord*. 2017;47:480–489.
86. Furber G, Leach M, Guy S, et al. Developing a broad categorisation scheme to describe risk factors for mental illness, for use in prevention policy and planning. *Australian New Zealand J Psychiatry*. 2017;51:230–240.
87. Sherwin E, Dinan TG, Cryan JF. Recent developments in understanding the role of the gut microbiota in brain health and disease. *Ann NY Acad Sci*. 2017 [Epub ahead of print]; DOI:10.1111/nyas.13416.
88. Dey M. Toward a personalized approach in prebiotics research. *Nutrients*. 2017;9:92.
89. Dinan TG, Cryan JF. Microbes, immunity, and behavior: psychoneuroimmunology meets the microbiome. *Neuropsychopharmacol Rev*. 2017;42:178–192.
90. Riglar DT, Giessen TW, Baym M, et al. Engineered bacteria can function in the mammalian gut long-term as live diagnostics of inflammation. *Nat Biotechnol*. 2017;35:653–658.
91. Suez J, Elinav E. The path towards microbiome-based metabolite treatment. *Nat Microbiol*. 2017;2:17075.
92. Browne HP, Neville BA, Forster SC, et al. Transmission of the gut microbiota: spreading of health. *Nat Rev Microbiol*. 2017;15:531–543.
93. Carroll IM, Ringel-Kulka T, Siddle JP, et al. Characterization of the fecal microbiota using high-throughput sequencing reveals a stable microbial community during storage. *PLoS One*. 2012;7:e46953.
94. Loomba R, Seguritan V, Li W, et al. Gut microbiome-based metagenomic signature for non-invasive detection of advanced fibrosis in human nonalcoholic fatty liver disease. *Cell Metab*. 2017;25:1054–1062.
95. Mirzaei MK, Maurice CF. Ménage à trois in the human gut: interactions between host, bacteria and phages. *Nat Rev Microbiol*. 2017;15:397–408.
96. Almonacid DE, Kraal L, Ossandon FJ, et al. 16S rRNA gene sequencing and healthy reference ranges for 28 clinically relevant microbial taxa from the human gut microbiome. *PLoS One*. 2017;12:e0176555.
97. Shankar V. Gut microbiome profiling tests propelled by customer demand. *Nat Biotechnol*. 2017;35:9.
98. Zaura E, Brandt BW, de Mattos MJT, et al. Same exposure but two radically different responses to antibiotics: resilience of the salivary microbiome versus long-term microbial shifts in feces. *mBio*. 2015;6:e01693–15.
99. Lim B, Zimmermann M, Barry NA, et al. Engineered regulatory systems modulate gene expression of human commensals in the gut. *Cell*. 2017;169:547–558.
100. Whitaker WR, Shepherd ES, Sonnenburg JL. Tunable expression tools enable single-cell strain distinction in the gut microbiome. *Cell*. 2017;169:538–546.
101. Lee CH, Steiner T, Petrof EO, et al. Frozen vs fresh fecal microbiota transplantation and clinical resolution of diarrhea in patients with recurrent *Clostridium difficile* infection. A randomized clinical trial. *JAMA*. 2016;315:142–149.
102. Wang B, Yao M, Lv L, et al. The human microbiota in health and disease. *Engineering*. 2017;3:71–82.
103. Staley C, Hamilton MJ, Vaughn BP, et al. Successful resolution of recurrent *Clostridium difficile* infection using freeze-dried, encapsulated fecal microbiota; Pragmatic cohort study. *Am J Gastroenterol*. 2017;112:940–947.
104. Vindigni SM, Surawicz CM. Fecal microbiota transplantation. *Gastroenterol Clin N Am*. 2017;46:171–185.
105. Jiang ZD, Ajami NL, Petrosino JF, et al. Randomised clinical trial: faecal microbiota transplantation for recurrent *Clostridium difficile* infection—fresh, or frozen, or lyophilised microbiota from a small pool of healthy donors delivered by colonoscopy. *Aliment Pharmacol Ther*. 2017;45:899–908.
106. Youngster I, Gerding DN. Making fecal microbiota transplantation easier to swallow: freeze-dried preparation for recurrent *Clostridium difficile* infections. *Am J Gastroenterol*. 2017;112:948–950.
107. Flowers SA, Evans SJ, Ward KM, et al. Interaction between atypical antipsychotics and the gut microbiome in a bipolar disease cohort. *Pharmacotherapy*. 2017;37:261–267.
108. Lee HJ, Choi JK, Ryu HS, et al. Therapeutic modulation of gut microbiota in functional bowel disorders. *J Neurogastroenterol Motil*. 2017;23:9–19.
109. Kazerouni A, Wein LM. Exploring the efficacy of pooled stools in fecal microbiota transplantation for microbiota-associated chronic diseases. *PLoS One*. 2017;12:e0163956.
110. Brennan CA, Garrett WS. Gut microbiota, inflammation, and colorectal cancer. *Annu Rev Microbiol*. 2016;70:395–411.

111. Fessler J, Gajewski TF. The microbiota: a new variable impacting cancer treatment outcomes. *Clin Cancer Res*. 2017 [Epub ahead of print]; DOI:10.1158/1078-0432.CCR-17-0864.
112. Tsuda A, Suda W, Morita H, et al. Influence of proton-pump inhibitors on the luminal microbiota in the gastrointestinal tract. *Clin Transl Gastroenterol*. 2015;6:e89.
113. Aagaard K, Ma J, Antony KM, et al. The placenta harbors a unique microbiome. *Sci Transl Med* 2014;6:237ra65.
114. Mor G, Kwon J-Y. Trophoblast-microbiome interaction: a new paradigm on immune regulation. *Am J Obstet Gynecol*. 2015;213:S131–S137.
115. Gomez-Arango LF, Barrett HL, McIntyre HD, et al. Antibiotic treatment at delivery shapes the initial oral microbiome in neonates. *Nat Sci Rep*. 2017;7:43481.
116. Mor G, Aldo P, Alvero AB. The unique immunological and microbial aspects of pregnancy. *Nat Rev Immunol*. 2017;17:469–482.
117. van Rensburg JJ, Lin H, Gao X, et al. The human skin microbiome associates with the outcome of and is influenced by bacterial infection. *mBio*. 2015;6:e01315-15.
118. Hassaneen M, Maron JL. Salivary diagnostics in pediatrics: applicability, translatability, and limitations. *Front Public Health*. 2017;5:83.
119. Simón-Soro Á, Tomás I, Cabrera-Rubio R, et al. Microbial geography of the oral cavity. *J Dent Res*. 2013;92:616–621.
120. Yu G, Phillips S, Gail MH, et al. Evaluation of buccal cell samples for studies of oral microbiota. *Cancer Epidemiol Biomarkers Prev*. 2017;26:249–253.
121. Zhang S, Cao X, Huang H. Sampling strategies for three-dimensional spatial community structures in IBD microbiota research. *Front Cell Infect Microbiol*. 2017;7:51.
122. Hall MW, Singh N, Ng KF, et al. Inter-personal diversity and temporal dynamics of dental, tongue, and salivary microbiota in the healthy oral cavity. *Nat Biofilms Microb*. 2017;3:2.
123. Proctor DM, Relman DA. The landscape ecology and microbiota of the human nose, mouth, and throat. *Cell Host Microbe*. 2017;21:421–432.
124. Simón-Soro Á, Mira A. Solving the etiology of dental caries. *Trends Microbiol*. 2015;23:76–82.
125. Krishnan K, Chen T, Paster BJ. A practical guide to the oral microbiome and its relation to health and disease. *Oral Dis*. 2017;23:276–286.
126. Zhang C-Z, Cheng X-Q, Li J-Y, et al. Saliva in the diagnosis of diseases. *Int J Oral Sci*. 2016;8:133–137.
127. Zhang Y, Sun J, Lin CC, et al. The emerging landscape of salivary diagnostics. *Periodontology* 2000. 2016;70:38–52.
128. Idris A, Hasnain SZ, Huat LZ, et al. Human diseases, immunity and the oral microbiota—Insights gained from metagenomic studies. *Oral Sci Int*. 2017;14:27–32.
129. Kaczor-Urbanowicz KE, Carreras-Presas CM, Aro K, et al. Saliva diagnostics—Current views and directions. *Exp Biol Med*. 2017;242:459–472.
130. Dewhirst FE, Chen T, Izard J, et al. The human oral microbiome. *J Bacteriol*. 2010;192:5002–5017.
131. Kilian M, Chapple ILC, Hannig M, et al. The oral microbiome—an update for oral healthcare professionals. *Br Dent J*. 2016;221:657–666.
132. Goodson JM, Hartman M-L, Shi P, et al. The salivary microbiome is altered in the presence of a high salivary glucose concentration. *PLoS One*. 2017;12:e0170437.
133. Li Y-H, Huang X, Tian X-L. Recent advances in dental biofilm: impacts of microbial interactions on the biofilm ecology and pathogenesis. *AIMS Bioeng*. 2017;4:335–350.
134. Akashi M, Tanaka K, Kusumoto J, et al. Brain abscess potentially resulting from odontogenic focus: report of three cases and a literature review. *J Maxillofac Oral Surg*. 2017;16:58–64.
135. Kaur H, Jain S, Shergill SK, et al. Unraveling the link between periodontal health and cardiovascular diseases. *J Dent Sci Oral Rehab*. 2016;7:28–35.
136. Koneru S, Rambabu T. Application of omics in personalized oral health care: a paradigm shift. *J Biomed Pharmaceut Res*. 2017;6:142–147.
137. Watts D. Scrutinising the link between periodontal disease and systemic conditions: does recent evidence continue to support the European Federation of Periodontology's 2012 Manifesto? *J Int Acad Periodontol*. 2017;19:36–41.
138. Blaser MJ. The theory of disappearing microbiota and the epidemics of chronic diseases. *Nat Rev Immunol*. 2017;17:461–463.
139. Llewelyn MJ, Fitzpatrick JM, Darwin E, et al. The antibiotic course has had its day. *Br Med J*. 2017;358:j3418.
140. Bhattacharya S, Rosenberg AF, Peterson DR, et al. Transcriptomic biomarkers to discriminate bacterial from nonbacterial infection in adults hospitalized with respiratory illness. *Nat Sci Rep*. 2017;7:6548.
141. Fontana CR, Abernethy AD, Som S, et al. The antibacterial effect of photodynamic therapy in dental plaque-derived biofilms. *J Periodont Res*. 2009;44:751–759.
142. Soukos NS, Goodson JM. Photodynamic therapy in the control of oral biofilms. *Periodontology* 2000. 2011;55:143–166.
143. Fontana CR, Song X, Polymeri A, et al. *Lasers Med Sci*. 2015;30:2077–2086.
144. Soukos NS, Stultz J, Abernethy AD, et al. Phototargeting human periodontal pathogens *in vivo*. *Lasers Med Sci*. 2015;30:943–952.
145. Tapio I, Shingfield KJ, McKain N, et al. Oral samples as non-invasive proxies for assessing the composition of the rumen microbial community. *PLoS One*. 2016;11:e0151220.
146. Ronquillo MG, Hernandez JCA. Antibiotic and synthetic growth promoters in animal diets: review of impact and analytical methods. *Food Control*. 2017;72:255–267.
147. Casewell M, Friis C, Marco E, et al. The European ban on growth-promoting antibiotics and emerging consequences for human and animal health. *J Antimicrob Chemother*. 2003;52:159–161.
148. Dai T. The antimicrobial effect of blue light: What are behind? *Virulence*. 2017;8:649–652.
149. Hughes G, Webber MA. Novel approaches to the treatment of bacterial biofilm infections. *Br J Pharmacol*. 2017;174:2237–2246.
150. Cameron SJS, Huws SA, Hegarty MJ, et al. The human salivary microbiome exhibits temporal stability in bacterial diversity. *FEMS Microbiol Ecol*. 2015;91:fiv091.
151. Belström D, Holmström P, Bardow A, et al. Temporal stability of the salivary microbiota in oral health. *PLoS One*. 2016;11:e0147472.
152. Zawadzki PJ, Perkowski K, Starościk B, et al. Identification of infectious microbiota from oral cavity environment of various population group patients as a preventive approach to human health risk factors. *Ann Agric Environ Med*. 2016;23:566–569.
153. Kinane DF, Stathopoulou PG, Papapanou PN. Periodontal diseases. *Nat Rev Dis Primers*. 2017;3:17038.
154. Arimatsu K, Yamada H, Miyazawa H, et al. Oral pathobiont induces systemic inflammation and metabolic changes associated with alteration of gut microbiota. *Nat Sci Rep*. 2014;4:4828.
155. Nakajima M, Arimatsu K, Kato T, et al. Oral administration of *P. gingivalis* induces dysbiosis of gut microbiota and impaired barrier function leading to dissemination of enterobacteria to the liver. *PLoS One*. 2015;10:e0134234.
156. Birchenough G, Hansson GC. Bacteria tell us how to protect our intestine. *Cell Host Microbe*. 2017;22:3–4.
157. Włodarska M, Luo C, Kolde R, et al. Indoleacrylic acid produced by commensal *Peptostreptococcus* species suppresses inflammation. *Cell Host Microbe*. 2017;22:25–37.
158. Grasset E, Puel A, Charpentier J, et al. A specific gut microbiota dysbiosis of type 2 diabetic mice induces GLP-1 resistance through an enteric NO-dependent and gut-brain axis mechanism. *Cell Metab*. 2017;25:1075–1090.
159. Stefanaki C, Peppas M, Mastorakos G, et al. Examining the gut bacteriome, virome, and mycobiome in glucose metabolism disorders: are we on the right track? *Metabolism*. 2017;73:52–66.
160. Xiao E, Mattos M, Vieira GHA, et al. Diabetes enhances IL-17 expression and alters the oral microbiome to increase its pathogenicity. *Cell Host Microbe*. 2017;22:120–128.
161. Tavares LJ, Pavarina AC, Vergani CE, et al. The impact of antimicrobial photodynamic therapy on peri-implant disease: what mechanisms are involved in this novel treatment? *Photodiagn Photodyn Ther*. 2017;17:236–244.
162. de Punder K, Pruimboom L. Stress induces endotoxemia and low-grade inflammation by increasing barrier permeability. *Front Immunol*. 2015;6:223.
163. Pereira PAB, Aho VTE, Paulin L, et al. Oral and nasal microbiota in Parkinson's disease. *Parkinsonism Relat Disord*. 2017;38:61–67.
164. Tremlett H, Bauer KC, Appel-Cresswell S, et al. The gut microbiome in human neurological disease: a review. *Ann Neurol*. 2017;81:369–382.
165. Stein SP, Steffen MJ, Smith C, et al. Serum antibodies to periodontal pathogens are a risk factor for Alzheimer's disease. *Alzheimer Dement*. 2012;8:196–203.
166. Chen B, Sun L, Zhang X. Integration of microbiome and epigenome to decipher the pathogenesis of autoimmune diseases. *J Autoimmun*. 2017;83:31–42.

167. Zhang X, Zhang D, Jia H, et al. The oral and gut microbiomes are perturbed in rheumatoid arthritis and partly normalized after treatment. *Nat Med*. 2015;21:895–905.
168. Vaghef-Mehrabany E, Alipour B, Homayouni-Rad A, et al. Probiotic supplementation improves inflammatory status in patients with rheumatoid arthritis. *Nutrition*. 2014;30:430–435.
169. Zamani B, Golkar HR, Farshbaf S, et al. Clinical and metabolic response to probiotic supplementation in patients with rheumatoid arthritis: a randomized, double-blind, placebo-controlled trial. *Int J Rheum Dis*. 2016;19:869–879.
170. González-Muniesa P, Martínez-González M-A, Hu FB, et al. Obesity. *Nat Rev Dis Primers*. 2017;3:17034.
171. Gregg EW, Shaw JE. Global health effects of overweight and obesity. *N Engl J Med*. 2017;377:80–81.
172. Alpizar-Rodríguez D, Finckh A. Environmental factors and hormones in the development of rheumatoid arthritis. *Semin Immunopathol*. 2017;39:461–468.
173. Chorzewski M, Orywal K, Sierpinska T, et al. Salivary protective factors in patients suffering from decompensated type 2 diabetes. *Adv Med Sci*. 2017;62:211–215.
174. Barratt MJ, Lebrilla C, Shapiro H-Y, et al. The gut microbiota, food science, and human nutrition: a timely marriage. *Cell Host Microbe*. 2017;22:134–141.
175. Green JM, Barratt MJ, Kinch M, et al. Food and microbiota in the FDA regulatory framework: how should microbiota-directed foods be regulated? *Science*. 2017;357:39–40.
176. Goutham G, Manikandan R, Beulaja M, et al. A focus on resveratrol and ocular problems, especially cataract: from chemistry to medical uses and clinical relevance. *Biomed Pharmacother*. 2017;86:232–241.
177. Horai R, Zárate-Bladés CR, Dillenburg-Pilla P, et al. Microbiota-dependent activation of an autoreactive T cell receptor provokes autoimmunity in an immunologically privileged site. *Immunity*. 2015;43:343–353.
178. Shin H, Price K, Albert L, et al. Changes in the eye microbiota associated with contact lens wearing. *mBio*. 2016;7:e00198-16.
179. St. Leger AJ, Desai JV, Drummond RA, et al. An ocular commensal protects against corneal infection by driving an interleukin-17 response from mucosal $\gamma\delta$ T cells. *Immunity*. 2017;47:148–158.
180. Zhang X, M VJ, Qu Y, et al. Dry eye management: targeting the ocular surface microenvironment. *Int J Mol Sci*. 2017;18:1398.
181. Nayfach S, Pollard KS. Toward accurate and quantitative comparative metagenomics. *Cell*. 2016;166:1103–1116.
182. Trøseid M. Gut microbiota and acute coronary syndromes: ready for use in the emergency room? *Eur Heart J*. 2017;38:825–827.

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Abbreviations Used

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

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