Chapter 20
Our Microbiome: On the Challenges, Promises, and Hype

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Abstract The microbiome field is increasingly raising interest among scientists, clinicians, biopharmaceutical entities, and the general public. Technological advances from the past two decades have enabled the rapid expansion of our ability to characterize the human microbiome in depth, highlighting its previously underappreciated role in contributing to multifactorial diseases including those with unknown etiology. Consequently, there is growing evidence that the microbiome could be utilized in medical diagnosis and patient stratification. Moreover, multiple gut microbes and their metabolic products may be bioactive, thereby serving as future potential microbiome-targeting or -associated therapeutics. Such therapies could include new generation probiotics, prebiotics, fecal microbiota transplantations, postbiotics, and dietary modulators. However, microbiome research has also been associated with significant limitations, technical and conceptual challenges, and, at times, "over-hyped" expectations that microbiome research will produce quick solutions to chronic and mechanistically complex human disorders. Herein, we summarize these challenges and also discuss some of the realistic promises associated with microbiome research and its applicability into clinical application.

Keywords Intestinal microbiome · Nutrition · Fecal microbiome transplant · Probiotics

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20.1 Introduction

The last decade was marked by an extraordinary number of reports discussing how microbiome composition associates with human health. Fewer studies have demonstrated its causal role in the pathogenesis of several conditions. The microbiome plasticity, contrasting with that of the human genome, renders it an attractive target for the development of therapeutics. However, microbiome research also suffers from a descriptive level of evidence, lack of causality, molecular-level understanding of mechanisms, and empiric evidence, leading to premature claims of microbiome-mediated treatments. Thus, there is a sharp contrast between public expectations and perception of the microbiome field to actual applications already available. This "hyper-hype" situation enables the bloom of unregulated and unsupervised microbiome-targeting therapeutics. In this perspective, we will discuss limitations, challenges, and potential solutions supporting the utilization of the microbiome in several clinical contexts. Transforming the microbiome field toward a molecular-level mechanistic understanding of its role in physiological and pathophysiological processes may lead to the development of robust medical exploitation of the ecosystem toward better diagnosis, prophylaxis, and treatment of a myriad of "multifactorial" disorders.

20.2 Promises in Microbiome Research

Beneficial modulation of the microbiome for therapeutic purposes is currently a major focus of translational research in the field. In this section, we will discuss recent advances, the level of evidence for each application, and challenges to be addressed before widespread implementation (Fig. 20.1). A hallmark of many of these approaches is microbiome heterogeneity in the human population and its related challenges and advantages.

20.2.1 Dietary and "Prebiotic" Microbiome Interventions

While most evidence point to the stability of the gut microbiome configuration in healthy adults (Mehta et al. 2018), diet is among the strongest microbiome modulators, with robust effects observed even following short exposure to an intervention (Sonnenburg et al. 2016). The relative ease of altering one's diet and reports on beneficial health outcomes in the host following diet-induced microbiome alterations (Anhê et al. 2017) render it an attractive therapeutic approach. Of the various microbiome-modulating nutrients, dietary fibers emerge as key players. Individuals consuming a fiber-rich diet harbor a higher abundance of bacteria producing short-chain fatty acids (SCFA), which lead to improved metabolic health parameters (Zhao

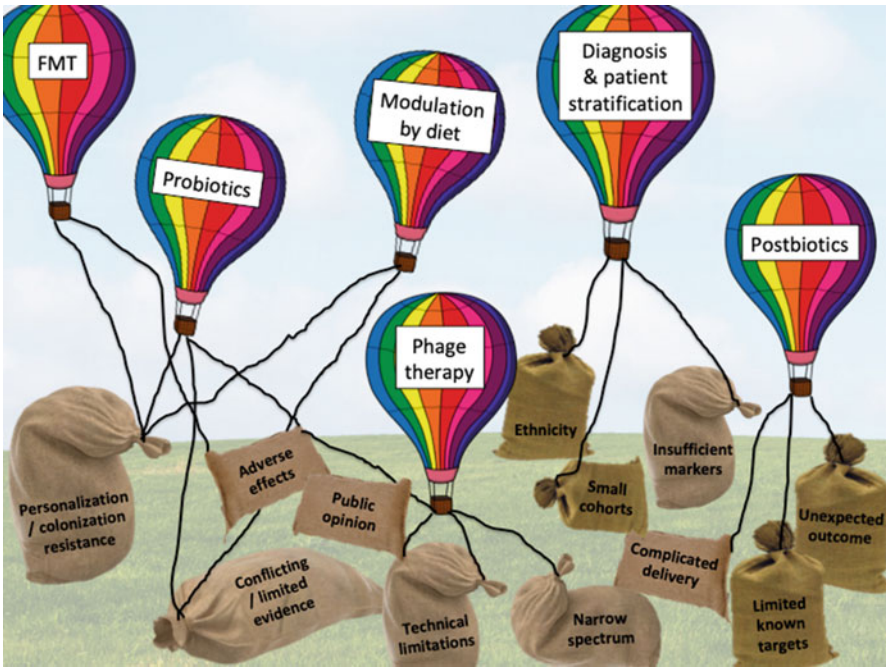

Fig. 20.1 Promises (balloons) and challenges (sacks) associated with microbiome research. The higher the balloon, the closest the applicability in the clinic

et al. 2018) and a beneficial outcome in IBD (Schroeder et al. 2018). Fibers could also improve gut barrier, either by restoring physical host–microbiome separation at the mucosal surface (Zou et al. 2018) or by correcting mucus layer defects (Schroeder et al. 2018), and protect against infections (Desai et al. 2016; Hryckowian et al. 2018). Nonetheless, dietary fiber may have a detrimental effect on hepatocellular carcinoma (Singh et al. 2018b). On the other side of the spectrum, significant reduction of carbohydrates to produce a ketogenic diet (KD) may be beneficial for the treatment of refractory epilepsy. This effect may be mediated by the microbiome, as KD promotes the bloom of *Akkermansia muciniphila* and *Parabacteroides spp.*, which were linked to systemic reductions in gamma-glutamylated amino acids, elevated hippocampal gamma-aminobutyric acid/glutamate levels, and consequently seizure protection (Olson et al. 2018). In addition to the nutrient balance of the diet, restricting the quantity and timing of feeding may beneficially affect the host through the microbiome. Individuals with obesity undergoing either short- (Dao et al. 2016) or long-term (Ruiz et al. 2017) caloric restriction diets experience a bloom of potentially beneficial taxa, and short-term restriction was also associated with improved insulin sensitivity. Microbiome transfer from mice undergoing experimental autoimmune encephalomyelitis and intermittent fasting ameliorated clinical score and spinal cord pathology; however, intermittent fasting did not improve clinical outcomes in individuals with multiple sclerosis (Cignarella

et al. 2018). Noteworthily, host responses and outcomes to the intake of identical diets can be affected by microbiome configuration (Dao et al. 2016; Korem et al. 2017), and the microbiome emerges as an important personalized feature that can improve the predictability of a diet outcome on the human health, superior to that based on the human genome (Rothschild et al. 2018). These observations lay the foundations to personally tailored, microbiome-based health-promoting diets (Zeevi et al. 2015).

20.2.2 Live Microbial Therapy (FMT and Probiotics)

One of the most promising translational achievements of microbiome research is the therapeutic application of fecal microbiome transplantation (FMT). Following its established efficacy in treating recurrent *Clostridium difficile* infections (van Nood et al. 2013), FMT has demonstrated efficacy against other antibiotic-resistant pathogens, including extended-spectrum beta-lactamase (ESBL) producers (Singh et al. 2018a) and vancomycin-resistant *Enterococcus* (VRE) (Caballero et al. 2017). Following antibiotics, autologous FMT rapidly restores mucosal microbiome composition and function in both the upper and lower gastrointestinal tract (Suez et al. 2018). FMT is also gaining attention as the means for correcting dysbiotic microbiome and treating other noninfectious conditions. In individuals with metabolic syndrome, insulin sensitivity is improved by FMT from lean donors, though the effect is abated after 18 weeks (Kootte et al. 2017). Allogeneic FMT also improves symptoms in the majority of patients with IBS (Mizuno et al. 2017; Johnsen et al. 2018), ulcerative colitis (Fuentes et al. 2017; Jacob et al. 2017), hepatic encephalopathy (Bajaj et al. 2017), as well as GI and behavioral symptoms in children with autistic spectrum disorders (Kang et al. 2017). Nonetheless, the aforementioned effects are transient and mostly observed only in some of the transplanted individuals. The majority of clinical trials with FMT correlate between the extent to which the recipient microbiome shifted toward the donor configuration and improvement of clinical parameters (Fuentes et al. 2017; Mizuno et al. 2017; Zuo et al. 2018), which in turn may be related to person-specific colonization resistance (Li et al. 2016), attributed in some works to pre-FMT microbiome configuration (Kootte et al. 2017). In order to circumvent this microbiome-conferred resistance, several trials have applied pre-FMT antibiotics and/or bowel lavage (Bajaj et al. 2017; Kang et al. 2017), although the contribution of these practices to the outcome is yet unclear. As a result, these treatments are currently not available to the public, and patients turn to homemade self-treatments, which expose them to potentially serious adverse effects.

A common additional live microbial therapy approach is the consumption of a limited consortium of so-called probiotic microorganisms, mostly from the *Lactobacillus* and *Bifidobacterium* genera. Despite decades of research, studies on health claims or probiotics are often contested due to conflicting reports, for example, recent publicly funded large-scale studies showing no beneficial effect in the context

of acute gastroenteritis (Freedman et al. 2018; Schnadower et al. 2018). Heterogeneity in therapeutic effects of probiotics may stem from variable capacity of probiotics to colonize the gut, either transiently during supplementation (Zmora et al. 2018) or in a persistent manner following cessation (Maldonado-Gómez et al. 2016; Zhang et al. 2016), as both were only observed in a subset of individuals (Zmora et al. 2018). Importantly, while fecal shedding does not reflect mucosal colonization, the fecal microbiome can be used to predict permissiveness or resistance to colonization (Zmora et al. 2018). Lack of colonization may limit the ability of probiotics to affect the gut microbiome (Zhang et al. 2016; Zmora et al. 2018), and both colonization and an effect on the microbiome may be required to produce a physiological effect in the context of experimental colitis (Suwal et al. 2018) or depression (Abildgaard et al. 2018). Colonization resistance to probiotics may be alleviated following antibiotics treatment, a common scenario in which probiotics are consumed as the means for the prevention of antibiotic-associated diarrhea and reconstitution of the pre-antibiotics configuration. Interestingly, rather than facilitating post-antibiotics microbiome reconstitution, probiotics may in fact delay the restoration of bacterial diversity in mice (Grazul et al. 2016; Suez et al. 2018) and in humans (Kabbani et al. 2017; Suez et al. 2018), which may explain some of the recent associations made between probiotics administered in the context of antibiotics and increased risk of infections (Spinler et al. 2016; Carvour et al. 2018; Oliveira and Widmer 2018).

To conclude, live microbial therapy is currently limited in efficacy. In parallel to addressing safety-related issues, through a better understanding of the interactions between the resident microbiome and supplemented microorganisms (either as probiotics or FMT) we can potentially tailor therapies that will bypass colonization resistance and successfully colonize the GI tract of the individual. An additional focus of research should be on the development of "new-generation probiotics," consisting of strains of gut-residing microbes that have shown benefits in pre-clinical models are being explored and tested in humans (O'Toole et al. 2017).

20.2.3 "Postbiotic" Approach

A more refined approach (termed "postbiotics") focuses on the administration of microbiome-derived bioactive molecules, which has the advantage of bypassing colonization resistance to the bacteria that express them. In addition, natural production of microbial metabolites often relies on the co-existence of a dietary nutrient (e.g., prebiotic fiber) and the presence of a metabolizing commensal, but the guts of individuals not harboring the commensal will not produce the metabolite. Administering the postbiotic product itself circumvents this personalization-related limitation. Noteworthy recent examples are as follows: flavonoid supplementation protected from diet-induced obesity (Thaiss et al. 2016); Muramyl dipeptide of Gram-positive bacteria reduced adipocyte inflammation and insulin tolerance in mice (Cavallari et al. 2017); and a membrane protein from *Akkermansia muciniphila*

improved metabolism in obese and diabetic mice (Plovier et al. 2017). Bioactive molecules can also target the microbiome, as demonstrated by inhibition of trimethylamine production by the administration of a choline analog, potentially reducing atherosclerosis risk (Roberts et al. 2018b).

Major challenges to this approach are understanding the response of the microbiome and the host to the postbiotic metabolite, which may disrupt natural regulatory circuits of its levels or activity, potentially leading to resistance or loss of natural production. The pharmacokinetics of the metabolite should be dissected or improved for it to reach the target site in active concentrations. As with other drugs, the metabolite should be stable and available for mass production.

20.2.4 Microbiome Engineering

Multiple approaches fall under this broad definition, including the targeted elimination of pathogens, pathobionts, or commensals, e.g., using bacteriophages, or the introduction of strains with a novel engineered trait. Few recent in vivo examples of the latter include strains engineered to increase the immune response to tumors (Zheng et al. 2017), or as biosensors to detect markers of inflammation in the gut (Riglar et al. 2017). Coadministering a nutrient that the strains have been engineered to exclusively utilize in the gut may assist in circumventing colonization resistance to the newly introduced strains (Shepherd et al. 2018).

Utilizing bacteriophages to eliminate pathogens has several advantages over antibiotics: reduced risk of promoting the spread of antibiotics resistance; specificity to a bacterial epitope, thus not disrupting the microbial community or the host; phage infection is self-limiting; and finally, the ease of isolating phages from the environment results in lower costs. Efficacy of phage therapy against multiple pathogens has so far been demonstrated in vivo, with few anecdotal case reports in humans and clinical trials performed thus far (Furfaro et al. 2018). This approach may be further broadened to eliminate pathobionts and commensals. Nonetheless, efficient phage therapy will require overcoming bacterial anti-phage resistance (Asija and Teschke 2018), which may benefit from better understanding or recently described phage-cooperation mechanisms (Erez et al. 2017; Borges et al. 2018; Landsberger et al. 2018).

20.3 Microbiome in Patient Stratification

Diverging from the generalized “one size fits all” approach, precision medicine strives to utilize individual-specific traits, measurements, and preferences in order to achieve improved efficacy and minimize side effects of treatment and prophylaxis modalities. Inter-individual variations in the presence, absence, and quantity of commensal microorganisms offer a formidable additional array of markers that can

be used for patient stratification or improved prophylaxis, with several notable advances made in recent years.

20.3.1 Microbiome as a Diagnostic Tool

The microbiome can harbor markers useful for early diagnosis and disease-risk prediction, superior to other, more invasive diagnostic tools. For example, children with a high risk for developing type 1 diabetes mellitus (T1DM) exhibit dysbiosis, decreased alpha diversity, and distinct microbiome-associated fecal and serum metabolites even before the overt manifestations of the disease (Vatanen et al. 2018). Levels of specific gut bacteria, including *Fusobacterium nucleatum*, could accurately distinguish between colorectal cancer patients and controls (Yu et al. 2017). In patients with nonalcoholic fatty liver disease, the microbiome can noninvasively classify advanced fibrosis or milder presentations (Loomba et al. 2017). In addition, microbial signatures can distinguish between patients with cirrhosis and early hepatocellular carcinoma (Ren et al. 2018b). In pediatric ulcerative colitis patients, microbiome markers were associated with remission, refractory disease, and severity (Schirmer et al. 2018). Translating these works into practice will require further validations in multiple cohorts, as well as identifying key taxonomic markers or metabolites from the gut microbiome.

20.3.2 A Drug for Each Bug?

Nonantibiotic drugs with a human target, especially proton-pump inhibitors and antipsychotics, can interact with the gut microbiome, potentially resulting in modulated activity or toxicity (Spanogiannopoulos et al. 2016; Maier et al. 2018). Prominent examples include the anti-diabetic drug Metformin, which was recently demonstrated to exert its beneficial effect by modulating the microbiome (Wu et al. 2017). Another example was recently described in the context of anti-Programmed cell death protein 1 (PD-1) checkpoint blockade immunotherapies, used as cancer therapies, but effective only in a subset of patients. Stratifying patients into "responders" and "nonresponders," specific microbiome signatures were found between these groups, with a causative role in mediating the effect of anti-PD1 therapy (Gopalakrishnan et al. 2018; Matson et al. 2018; Routy et al. 2018). Understanding drug–microbiome interactions could enable us to better choose between existing therapies and identify microorganisms or metabolites that may be used as novel adjuvants to improve drug efficacies.

20.4 Limitations and Challenges in Microbiome Research

In addition to challenges specific to each translational aspect of microbiome research noted above, there are further limitations to consider when addressing basic science questions in the young and still-developing field of microbiome research (Fig. 20.1).

20.4.1 Effect of Ethnicity and Geography

The majority of trials studying the role of the microbiome in human health have thus far focused on individuals from industrialized societies. However, differences in diets between individuals and populations play a major role in distinguishing between their respective microbiomes, as it was observed studying microbiome from hunter-gatherers (Smits et al. 2017), and U.S. immigrants (Vangay et al. 2018). The contribution of diet was challenged by the notion that microbiome composition of vegans and carnivores in an urban environment in USA is similar (Wu et al. 2016) although this lack of distinction was hypothesized to stem from broad dietary regimen descriptions (e.g., vegan) not being sufficiently descriptive of the diet contents. When the amount of consumed plant material is taken into consideration, the effect of diet is observed (McDonald et al. 2018). Indeed, disentangling ethnicity, diet, lifestyle, and genetics is not a trivial task, especially if small groups residing in distinct regions are characterized. A study of more than 2000 adults from six ethnicities living in Amsterdam identified an effect of ethnicity on the microbiome configuration, which was also partly explained by diet or lifestyle alone (Deschasaux et al. 2018). Confounding effects of ethnicity or geographical location on microbiome configuration may be an important limitation when developing diagnostics based on microbial markers. A study encompassing 7000 individuals from 14 districts in China found that geographical signature on the microbiome surpassed that of conditions such as type-2 diabetes, metabolic syndrome, and fatty liver. Consequently, machine-learning algorithms for the prediction of disease status performed poorly when applied to a population geographically distinct than the one used for training the predictor (He et al. 2018). It is, therefore, crucial to increase the diversity of sampled cohort, not only to improve patient stratification but also to potentially recognize human ancestral health-promoting commensals that may have been lost due to industrialization (Bello et al. 2018).

20.4.2 Neglected Omes: Nonbacterial Microbiomes

Improved sequencing technologies now enable better characterization of nonbacterial members of the microbial community. The virome may affect human health and serve as a biomarker of disease. Successful treatment of CDI by sterile

fecal filtrate suggests a protective role of the virome against *C. difficile* (Ott et al. 2017), and in another pilot study, FMT performed in CDI resulted in a successful outcome only in the case of high richness of the recipients' virome (Zuo et al. 2018). Enteric viruses may elicit protective immunity during gut inflammation and ameliorate colitis (Yang et al. 2016). Characterization of the gut mycome is still challenging, due to great variability in the outcome with different extraction methods, as well as poor annotation of the current fungal databases (Vesty et al. 2017). The mycome has been receiving attention as a potential marker for IBD, but with inconsistent results (Hoarau et al. 2016; Liguori et al. 2016; Sokol et al. 2017). Importantly, the mycome may exert its effects on the host through interaction with the bacterial domain (Hoarau et al. 2016). There is a great need in expanding our understanding of the nonbacterial microbiome and unlock its therapeutic potential.

20.4.3 Extraintestinal Microbiomes

Commensal bacteria may be found in any environment-associated niche of the host and were even suggested to be present in the placenta (Collado et al. 2016; Parnell et al. 2017) and the brain (Roberts et al. 2018a) although the former was recently refuted (Leiby et al. 2018). An analysis of six distinct body sites of healthy humans demonstrated temporal stability (Lloyd-Price et al. 2017), though pathology-associated shifts may occur. *Fusobacterium nucleatum*, a pathobiont of the oral microbiome, was shown to inhibit human T cell response in CRC (Nosho 2016); several studies suggested *Fusobacterium* as a good diagnostic marker for CRC, either quantifying the bacterium itself (Wong et al. 2017; Guo et al. 2018) or serum antibodies against it (Wang et al. 2016). DOCK8 deficiency causes in humans recurrent skin infections; recent metagenomic analyses of the skin virome of these patients revealed an increase in papillomavirus sequences, pointing toward the importance of biosurveillance over viral microorganisms in genetically susceptible individuals (Tirosh et al. 2018). Recently, an association was found among disease exacerbation, Th17 response, and highly transcriptionally active *Streptococcus* and *Pseudomonas* in COPD patients (Ren et al. 2018a).

20.4.4 Technical Limitations

While designing and interpreting microbiome-related trials, the following should be considered. First, the descriptive nature of the majority of microbiome studies does not enable to distinguish between incidences in which the microbiome has a causative role in a phenotype and passenger effects. Causality may be demonstrated through recapitulating a phenotype by transferring the microbial community in question to a naive animal, or the microbe-produced metabolites. Quantifying relative abundances of bacteria can be misleading, as an increase in the relative

abundance of a taxon could reflect the decrease in other commensals rather than an absolute increase in the abundance of a specific bacterium in question, and differences in microbial load among samples can produce bias in the relative quantification (Gloor et al. 2017). Genuine bacterial quantification in a sample can be achieved through qPCR, statistical algorithms (Rothschild et al. 2018), or combining DNA sequencing with flow cytometry for enumeration (Vandeputte et al. 2017). Differences in the sequencing and computational analysis pipeline can lead to different results. Analyses of 16s rDNA is a well-tested, cost-effective technology that enables to obtain a taxonomic resolution of the microbiome composition. However, it bears some important limitations such as providing bacterial identity solely at the genus level, and being prone to biases due to over-amplification or diverse affinity of the primers for different species. New algorithms utilizing error profiles, such as DADA2 and Deblur, now enable higher resolution analyses (Callahan et al. 2016; Amir et al. 2017). In addition, taxonomic assignment is highly dependent on reference databases, which are incomplete. Shotgun metagenomics analysis provides considerably more information, including functional insights and strain-level resolution; however, it is also prone to bias, mostly due to the impact of the DNA extraction method (Costea et al. 2017).

20.5 Conclusions and Prospects

The aforementioned challenges may seem to be discouraging, yet they may serve as a guide that distinguishes between microbiome-related discoveries that are already or will potentially be ripe for clinical application in the near future, to basic science questions that still lack fundamental elements before they can be applied. Of the aforementioned, microbiome targeting through FMT or probiotics is already practiced although both methods are associated with inconsistent reports of efficacy for multiple conditions. There is a great need for additional clinical trials with FMT, as well as nonbiased, publicly funded trials regarding probiotics, yet both methods are likely to benefit from identifying factors mediating colonization resistance and how to circumvent it. Integrating the microbiome to precision medicine can assist in improving diagnosis, prophylaxis, and prognosis, but thus far is unrealistic on a broad scale due to the cost of sequencing an individual's microbiome and the complexity of the analysis. In addition, it is crucial to identify markers that are applicable across distinct populations. Basic science questions remain to be addressed before other therapeutic approaches, including postbiotics supplement, microbiome engineering, and phage therapy, are proven to be safe and efficacious. Importantly, maintaining an effect of microbiome-based therapies may be affected by the host genetics, diet, or lifestyle (Kootte et al. 2017; Smits et al. 2018). Thus, the microbiome may serve as the first step for disease amelioration, but long-term maintenance requires further adaptations from the patient's side.

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References

Abildgaard A, Kern T, Pedersen O, Hansen T, Wegener G, Lund S (2018) The antidepressant-like effect of probiotics and their faecal abundance may be modulated by the cohabiting gut microbiota in rats. Eur Neuropsychopharmacol 29(1):98–110. https://doi.org/10.1016/j.euroneuro.2018.10.011

Amir A, McDonald D, Navas-Molina JA, Kopylova E, Morton JT, Zech Xu Z, Kightley EP, Thompson LR, Hyde ER, Gonzalez A, Knight R (2017) Deblur rapidly resolves single-nucleotide community sequence patterns. mSystems 2:e00191-16. https://doi.org/10.1128/mSystems.00191-16

Anhê FF, Nachbar RT, Varin TV, Vilela V, Dudonné S, Pilon G, Fournier M, Lecours M-A, Desjardins Y, Roy D, Levy E, Marette A (2017) A polyphenol-rich cranberry extract reverses insulin resistance and hepatic steatosis independently of body weight loss. Mol Metab 6:1563–1573. https://doi.org/10.1016/j.molmet.2017.10.003

Asija K, Teschke CM (2018) Lessons from bacteriophages part 2: a saga of scientific breakthroughs and prospects for their use in human health. PLoS Pathog 14:e1006970. https://doi.org/10.1371/journal.ppat.1006970

Bajaj JS, Kassam Z, Fagan A, Gavis EA, Liu E, Cox IJ, Kheradman R, Heuman D, Wang J, Gurry T, Williams R, Sikaroodi M, Fuchs M, Alm E, John B, Thacker LR, Riva A, Smith M, Taylor-Robinson SD, Gillevet PM (2017) Fecal microbiota transplant from a rational stool donor improves hepatic encephalopathy: a randomized clinical trial. Hepatology 66:1727–1738. https://doi.org/10.1002/hep.29306

Bello MGD, Knight R, Gilbert JA, Blaser MJ (2018) Preserving microbial diversity. Science 362:33–34. https://doi.org/10.1126/science.aau8816

Borges AL, Zhang JY, Rollins MF, Osuna BA, Wiedenheft B, Bondy-Denomy J (2018) Bacteriophage Cooperation Suppresses CRISPR-Cas3 and Cas9 Immunity. Cell 174:917–925. https://doi.org/10.1016/j.cell.2018.06.013

Caballero S, Kim S, Carter RA, Leiner IM, Sušac B, Miller L, Kim GJ, Ling L, Pamer EG (2017) Cooperating commensals restore colonization resistance to vancomycin-resistant enterococcus faecium. Cell Host Microbe 21:592–602.e4. https://doi.org/10.1016/j.chom.2017.04.002

Callahan BJ, McMurdie PJ, Rosen MJ, Han AW, Johnson AJA, Holmes SP (2016) DADA2: high-resolution sample inference from Illumina amplicon data. Nat Methods 13:581–583. https://doi.org/10.1038/nmeth.3869

Carvour ML, Wilder SL, Ryan KL, Walraven C, Qeadan F, Brett M, Page K (2018) Predictors of Clostridium difficile infection and predictive impact of probiotic use in a diverse hospital-wide cohort. Am J Infect Control 47:2–8. https://doi.org/10.1016/j.ajic.2018.07.014

Cavallari JF, Fullerton MD, Duggan BM, Foley KP, Denou E, Smith BK, Desjardins EM, Henriksbo BD, Kim KJ, Tuinema BR, Stearns JC, Prescott D, Rosenstiel P, Coombes BK, Steinberg GR, Schertzer JD (2017) Muramyl dipeptide-based postbiotics mitigate obesity-induced insulin resistance via IRF4. Cell Metab 25:1063–1074.e3. https://doi.org/10.1016/j.cmet.2017.03.021

Cignarella F, Cantoni C, Ghezzi L, Salter A, Dorsett Y, Chen L, Phillips D, Weinstock GM, Fontana L, Cross AH, Zhou Y, Piccio L (2018) Intermittent fasting confers protection in CNS autoimmunity by altering the gut microbiota. Cell Metab 27:1222–1235.e6. https://doi.org/10.1016/j.cmet.2018.05.006

Collado MC, Rautava S, Aakko J, Isolauri E, Salminen S (2016) Human gut colonisation may be initiated in utero by distinct microbial communities in the placenta and amniotic fluid. Sci Rep 6:23129

Costea PI, Zeller G, Sunagawa S, Pelletier E, Alberti A, Levenez F, Tramontano M, Driessen M, Hercog R, Jung F-E, Kultima JR, Hayward MR, Coelho LP, Allen-Vercoe E, Bertrand L, Blaut M, Brown JRM, Carton T, Cools-Portier S, Daigneault M, Derrien M, Druesne A, de Vos WM, Finlay BB, Flint HJ, Guarner F, Hattori M, Heilig H, Luna RA, van Hylckama VJ, Junick J, Klymiuk I, Langella P, Le Chatelier E, Mai V, Manichanh C, Martin JC, Mery C, Morita H, O'Toole PW, Orvain C, Patil KR, Penders J, Persson S, Pons N, Popova M, Salonen A, Saulnier D, Scott KP, Singh B, Slezak K, Veiga P, Versalovic J, Zhao L, Zoetendal EG, Ehrlich SD, Dore J, Bork P (2017) Towards standards for human fecal sample processing in metagenomic studies. Nat Biotechnol 35:1069

Dao MC, Everard A, Aron-Wisnewsky J, Sokolovska N, Prifti E, Verger EO, Kayser BD, Levenez F, Chilloux J, Hoyles L, Dumas M-E, Rizkalla SW, Doré J, Cani PD, Clément K, MICRO-Obes Consortium, Dumas M-E, Rizkalla SW, Doré J, Cani PD, Clément K (2016) Akkermansia muciniphila and improved metabolic health during a dietary intervention in obesity: relationship with gut microbiome richness and ecology. Gut 65:426–436. https://doi.org/10.1136/gutjnl-2014-308778

Desai MS, Seekatz AM, Koropatkin NM, Kamada N, Hickey CA, Wolter M, Pudlo NA, Kitamoto S, Terrapon N, Muller A, Young VB, Henrissat B, Wilmes P, Stappenbeck TS, Núñez G, Martens EC (2016) A dietary fiber-deprived gut microbiota degrades the colonic mucus barrier and enhances pathogen susceptibility. Cell 167:1339–1353.e21. https://doi.org/10.1016/j.cell.2016.10.043

Deschasaux M, Bouter KE, Prodan A, Levin E, Groen AK, Herrema H, Tremaroli V, Bakker GJ, Attaye I, Pinto-Sietsma S-J, van Raalte DH, Snijder MB, Nicolaou M, Peters R, Zwinderman AH, Bäckhed F, Nieuwdorp M (2018) Depicting the composition of gut microbiota in a population with varied ethnic origins but shared geography. Nat Med 24:1526–1531. https://doi.org/10.1038/s41591-018-0160-1

Erez Z, Steinberger-Levy I, Shamir M, Doron S, Stokar-Avihail A, Peleg Y, Melamed S, Leavitt A, Savidor A, Albeck S, Amitai G, Sorek R (2017) Communication between viruses guides lysis-lysogeny decisions. Nature 541:488–493. https://doi.org/10.1038/nature21049

Freedman SB, Williamson-Urquhart S, Farion KJ, Gouin S, Willan AR, Poonai N, Hurley K, Sherman PM, Finkelstein Y, Lee BE, Pang X-L, Chui L, Schnadower D, Xie J, Gorelick M, Schuh S, PERC PROGUT Trial Group (2018) Multicenter trial of a combination probiotic for children with gastroenteritis. N Engl J Med 379:2015–2026. https://doi.org/10.1056/NEJMoa1802597

Fuentes S, Rossen NG, van der Spek MJ, Hartman JH, Huuskonen L, Korpela K, Salojärvi J, Aalvink S, de Vos WM, D'Haens GR, Zoetendal EG, Ponsioen CY (2017) Microbial shifts and

signatures of long-term remission in ulcerative colitis after faecal microbiota transplantation. ISME J 11:1877–1889. https://doi.org/10.1038/ismej.2017.44

Furfaro LL, Payne MS, Chang BJ (2018) Bacteriophage therapy: clinical trials and regulatory hurdles. Front Cell Infect Microbiol 8:376. https://doi.org/10.3389/fcimb.2018.00376

Gloor GB, Macklaim JM, Pawlowsky-Glahn V, Egozcue JJ (2017) Microbiome datasets are compositional: and this is not optional. Front Microbiol 8:2224. https://doi.org/10.3389/fmicb.2017.02224

Gopalakrishnan V, Spencer CN, Nezi L, Reuben A, Andrews MC, Karpinets TV, Prieto PA, Vicente D, Hoffman K, Wei SC, Cogdill AP, Zhao L, Hudgens CW, Hutchinson DS, Manzo T, Petaccia de Macedo M, Cotechini T, Kumar T, Chen WS, Reddy SM, Szczepaniak Sloane R, Galloway-Pena J, Jiang H, Chen PL, Shpall EJ, Rezvani K, Alousi AM, Chemaly RF, Shelburne S, Vence LM, Okhuysen PC, Jensen VB, Swennes AG, McAllister F, Marcelo Riquelme Sanchez E, Zhang Y, Le Chatelier E, Zitvogel L, Pons N, Austin-Breneman JL, Haydu LE, Burton EM, Gardner JM, Sirmans E, Hu J, Lazar AJ, Tsujikawa T, Diab A, Tawbi H, Glitza IC, Hwu WJ, Patel SP, Woodman SE, Amaria RN, Davies MA, Gershenwald JE, Hwu P, Lee JE, Zhang J, Coussens LM, Cooper ZA, Futreal PA, Daniel CR, Ajami NJ, Petrosino JF, Tetzlaff MT, Sharma P, Allison JP, Jenq RR, Wargo JA (2018) Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. Science 359:97–103. https://doi.org/10.1126/science.aan4236

Grazul H, Kanda LL, Gondek D (2016) Impact of probiotic supplements on microbiome diversity following antibiotic treatment of mice. Gut Microbes 7:101–114. https://doi.org/10.1080/19490976.2016.1138197

Guo S, Li L, Xu B, Li M, Zeng Q, Xiao H, Xue Y, Wu Y, Wang Y, Liu W, Zhang G (2018) A simple and novel fecal biomarker for colorectal cancer: ratio of fusobacterium nucleatum to probiotics populations, based on their antagonistic effect. Clin Chem 64:1327–1337. https://doi.org/10.1373/clinchem.2018.289728

He Y, Wu W, Zheng H-M, Li P, McDonald D, Sheng H-F, Chen M-X, Chen Z-H, Ji G-Y, Zheng Z-D-X, Mujagond P, Chen X-J, Rong Z-H, Chen P, Lyu L-Y, Wang X, Wu C-B, Yu N, Xu Y-J, Yin J, Raes J, Knight R, Ma W-J, Zhou H-W (2018) Regional variation limits applications of healthy gut microbiome reference ranges and disease models. Nat Med 24:1532–1535. https://doi.org/10.1038/s41591-018-0164-x

Hoarau G, Mukherjee PK, Gower-Rousseau C, Hager C, Chandra J, Retuerto MA, Neut C, Vermeire S, Clemente J, Colombel JF, Fujioka H, Poulain D, Sendid B, Ghannoum MA (2016) Bacteriome and mycobiome interactions underscore microbial dysbiosis in familial Crohn's disease. MBio 7:e01250-16. https://doi.org/10.1128/mBio.01250-16

Hryckowian AJ, Van Treuren W, Smits SA, Davis NM, Gardner JO, Bouley DM, Sonnenburg JL (2018) Microbiota-accessible carbohydrates suppress Clostridium difficile infection in a murine model. Nat Microbiol 3:662–669. https://doi.org/10.1038/s41564-018-0150-6

Jacob V, Crawford C, Cohen-Mekelburg S, Viladomiu M, Putzel GG, Schneider Y, Chabouni F, O'Neil S, Bosworth B, Woo V, Ajami NJ, Petrosino JF, Gerardin Y, Kassam Z, Smith M, Iliev ID, Sonnenberg GF, Artis D, Scherl E, Longman RS (2017) Single delivery of high-diversity fecal microbiota preparation by colonoscopy is safe and effective in increasing microbial diversity in active ulcerative colitis. Inflamm Bowel Dis 23:903–911. https://doi.org/10.1097/MIB.0000000000001132

Johnsen PH, Hilpüsch F, Cavanagh JP, Leikanger IS, Kolstad C, Valle PC, Goll R (2018) Faecal microbiota transplantation versus placebo for moderate-to-severe irritable bowel syndrome: a double-blind, randomised, placebo-controlled, parallel-group, single-centre trial. lancet. Gastroenterol Hepatol 3:17–24. https://doi.org/10.1016/S2468-1253(17)30338-2

Kabbani TA, Pallav K, Dowd SE, Villafuerte-Galvez J, Vanga RR, Castillo NE, Hansen J, Dennis M, Leffler DA, Kelly CP (2017) Prospective randomized controlled study on the effects of Saccharomyces boulardii CNCM I-745 and amoxicillin-clavulanate or the combination on the gut microbiota of healthy volunteers. Gut Microbes 8:17–32. https://doi.org/10.1080/19490976.2016.1267890

Kang D-W, Adams JB, Gregory AC, Borody T, Chittick L, Fasano A, Khoruts A, Geis E, Maldonado J, McDonough-Means S, Pollard EL, Roux S, Sadowsky MJ, Lipson KS, Sullivan MB, Caporaso JG, Krajmalnik-Brown R (2017) Microbiota Transfer Therapy alters gut ecosystem and improves gastrointestinal and autism symptoms: an open-label study. Microbiome 5:10. https://doi.org/10.1186/s40168-016-0225-7

Kootte RS, Levin E, Salojärvi J, Smits LP, Hartstra AV, Udayappan SD, Hermes G, Bouter KE, Koopen AM, Holst JJ, Knop FK, Blaak EE, Zhao J, Smidt H, Harms AC, Hankemeijer T, Bergman JJGHM, Romijn HA, Schaap FG, Olde Damink SWM, Ackermans MT, Dallinga-Thie GM, Zoetendal E, de Vos WM, Serlie MJ, Stroes ESG, Groen AK, Nieuwdorp M (2017) Improvement of insulin sensitivity after lean donor feces in metabolic syndrome is driven by baseline intestinal microbiota composition. Cell Metab 26:611–619.e6. https://doi.org/10.1016/j.cmet.2017.09.008

Korem T, Zeevi D, Zmora N, Weissbrod O, Bar N, Lotan-Pompan M, Avnit-Sagi T, Kosower N, Malka G, Rein M, Suez J, Goldberg BZ, Weinberger A, Levy AA, Elinav E, Segal E (2017) Bread affects clinical parameters and induces gut microbiome-associated personal glycemic responses. Cell Metab 25:1243–1253. https://doi.org/10.1016/j.cmet.2017.05.002

Landsberger M, Gandon S, Meaden S, Rollie C, Chevallereau A, Chabas H, Buckling A, Westra ER, van Houte S (2018) Anti-CRISPR phages cooperate to overcome CRISPR-cas immunity. Cell 174:908–916. https://doi.org/10.1016/j.cell.2018.05.058

Leiby JS, McCormick K, Sherrill-Mix S, Clarke EL, Kessler LR, Taylor LJ, Hofstaedter CE, Roche AM, Mattei LM, Bittinger K, Elovitz MA, Leite R, Parry S, Bushman FD (2018) Lack of detection of a human placenta microbiome in samples from preterm and term deliveries. Microbiome 6:196. https://doi.org/10.1186/s40168-018-0575-4

Li SS, Zhu A, Benes V, Costea PI, Hercog R, Hildebrand F, Huerta-Cepas J, Nieuwdorp M, Salojärvi J, Voigt AY, Zeller G, Sunagawa S, de Vos WM, Bork P (2016) Durable coexistence of donor and recipient strains after fecal microbiota transplantation. Science 352:586–589. https://doi.org/10.1126/science.aad8852

Liguori G, Lamas B, Richard ML, Brandi G, da Costa G, Hoffmann TW, Di Simone MP, Calabrese C, Poggioli G, Langella P, Campieri M, Sokol H (2016) Fungal dysbiosis in mucosa-associated microbiota of Crohn's disease patients. J Crohn's Colitis 10:296–305. https://doi.org/10.1093/ecco-jcc/jjv209

Lloyd-Price J, Mahurkar A, Rahnavard G, Crabtree J, Orvis J, Hall AB, Brady A, Creasy HH, McCracken C, Giglio MG, McDonald D, Franzosa EA, Knight R, White O, Huttenhower C (2017) Strains, functions and dynamics in the expanded human microbiome project. Nature 550:61

Loomba R, Seguritan V, Li W, Long T, Klitgord N, Bhatt A, Dulai PS, Caussy C, Bettencourt R, Highlander SK, Jones MB, Sirlin CB, Schnabl B, Brinkac L, Schork N, Chen C-H, Brenner DA, Biggs W, Yooseph S, Venter JC, Nelson KE (2017) Gut microbiome-based metagenomic signature for non-invasive detection of advanced fibrosis in human nonalcoholic fatty liver disease. Cell Metab 25:1054–1062.e5. https://doi.org/10.1016/j.cmet.2017.04.001

Maier L, Pruteanu M, Kuhn M, Zeller G, Telzerow A, Anderson EE, Brochado AR, Fernandez KC, Dose H, Mori H, Patil KR, Bork P, Typas A (2018) Extensive impact of non-antibiotic drugs on human gut bacteria. Nature 555:623–628. https://doi.org/10.1038/nature25979

Maldonado-Gómez MX, Martínez I, Bottacini F, O'Callaghan A, Ventura M, van Sinderen D, Hillmann B, Vangay P, Knights D, Hutkins RW, Walter J (2016) Stable engraftment of bifidobacterium longum AH1206 in the human gut depends on individualized features of the resident microbiome. Cell Host Microbe 20:515–526. https://doi.org/10.1016/j.chom.2016.09.001

Matson V, Fessler J, Bao R, Chongsuwat T, Zha Y, Alegre M-L, Luke JJ, Gajewski TF (2018) The commensal microbiome is associated with anti-PD-1 efficacy in metastatic melanoma patients. Science 359:104–108. https://doi.org/10.1126/science.aao3290

McDonald D, Hyde E, Debelius JW, Morton JT, Gonzalez A, Ackermann G, Aksenov AA, Behsaz B, Brennan C, Chen Y, DeRight GL, Dorrestein PC, Dunn RR, Fahimipour AK,

Gaffney J, Gilbert JA, Gogul G, Green JL, Hugenholtz P, Humphrey G, Huttenhower C, Jackson MA, Janssen S, Jeste DV, Jiang L, Kelley ST, Knights D, Kosciolek T, Ladau J, Leach J, Marotz C, Meleshko D, Melnik AV, Metcalf JL, Mohimani H, Montassier E, Navas-Molina J, Nguyen TT, Peddada S, Pevzner P, Pollard KS, Rahnavard G, Robbins-Pianka A, Sangwan N, Shorenstein J, Smarr L, Song SJ, Spector T, Swafford AD, Thackray VG, Thompson LR, Tripathi A, Vázquez-Baeza Y, Vrbanac A, Wischmeyer P, Wolfe E, Zhu Q, Knight R (2018) American gut: an open platform for citizen science microbiome research. mSystems 3:e00031-18

Mehta RS, Abu-Ali GS, Drew DA, Lloyd-Price J, Subramanian A, Lochhead P, Joshi AD, Ivey KL, Khalili H, Brown GT, DuLong C, Song M, Nguyen LH, Mallick H, Rimm EB, Izard J, Huttenhower C, Chan AT (2018) Stability of the human faecal microbiome in a cohort of adult men. Nat Microbiol 3:347–355. https://doi.org/10.1038/s41564-017-0096-0

Mizuno S, Masaoka T, Naganuma M, Kishimoto T, Kitazawa M, Kurokawa S, Nakashima M, Takeshita K, Suda W, Mimura M, Hattori M, Kanai T (2017) Bifidobacterium-rich fecal donor may be a positive predictor for successful fecal microbiota transplantation in patients with irritable bowel syndrome. Digestion 96:29–38. https://doi.org/10.1159/000471919

Nosho K (2016) Association of Fusobacterium nucleatum with immunity and molecular alterations in colorectal cancer. World J Gastroenterol 22:557. https://doi.org/10.3748/wjg.v22.i2.557

O'Toole PW, Marchesi JR, Hill C (2017) Next-generation probiotics: the spectrum from probiotics to live biotherapeutics. Nat Microbiol 2:17057

Oliveira BCM, Widmer G (2018) Probiotic product enhances susceptibility of mice to cryptosporidiosis. Appl Environ Microbiol 84(21):e01408-18. https://doi.org/10.1128/AEM.01408-18

Olson CA, Vuong HE, Yano JM, Liang QY, Nusbaum DJ, Hsiao EY (2018) The gut microbiota mediates the anti-seizure effects of the ketogenic diet. Cell 174:497. https://doi.org/10.1016/j.cell.2018.06.051

Ott SJ, Waetzig GH, Rehman A, Moltzau-Anderson J, Bharti R, Grasis JA, Cassidy L, Tholey A, Fickenscher H, Seegert D, Rosenstiel P, Schreiber S (2017) Efficacy of sterile fecal filtrate transfer for treating patients with clostridium difficile infection. Gastroenterology 152:799–811.e7. https://doi.org/10.1053/j.gastro.2016.11.010

Parnell LA, Briggs CM, Cao B, Delannoy-Bruno O, Schrieffer AE, Mysorekar IU (2017) Microbial communities in placentas from term normal pregnancy exhibit spatially variable profiles. Sci Rep 7:11200. https://doi.org/10.1038/s41598-017-11514-4

Plovier H, Everard A, Druart C, Depommier C, Van Hul M, Geurts L, Chilloux J, Ottman N, Duparc T, Lichtenstein L, Myridakis A, Delzenne NM, Klievink J, Bhattacharjee A, van der Ark KCH, Aalvink S, Martinez LO, Dumas M-E, Maiter D, Loumaye A, Hermans MP, Thissen J-P, Belzer C, de Vos WM, Cani PD (2017) A purified membrane protein from Akkermansia muciniphila or the pasteurized bacterium improves metabolism in obese and diabetic mice. Nat Med 23:107–113. https://doi.org/10.1038/nm.4236

Ren L, Zhang R, Rao J, Xiao Y, Zhang Z, Yang B, Cao D, Zhong H, Ning P, Shang Y, Li M, Gao Z, Wang J (2018a) Transcriptionally active lung microbiome and its association with bacterial biomass and host inflammatory status. mSystems 3:e00199-18

Ren Z, Li A, Jiang J, Zhou L, Yu Z, Lu H, Xie H, Chen X, Shao L, Zhang R, Xu S, Zhang H, Cui G, Chen X, Sun R, Wen H, Lerut JP, Kan Q, Li L, Zheng S (2018b) Gut microbiome analysis as a tool towards targeted non-invasive biomarkers for early hepatocellular carcinoma. Gut. https://doi.org/10.1136/gutjnl-2017-315084

Riglar DT, Giessen TW, Baym M, Kerns SJ, Niederhuber MJ, Bronson RT, Kotula JW, Gerber GK, Way JC, Silver PA (2017) Engineered bacteria can function in the mammalian gut long-term as live diagnostics of inflammation. Nat Biotechnol 35:653–658. https://doi.org/10.1038/nbt.3879

Roberts C, Farmer CB, Walter CK (2018a) The human brain microbiome; there are bacteria in our brains! Birmingham, AL, Psychiatry Behav Neurobio, Univ Alabama

Roberts AB, Gu X, Buffa JA, Hurd AG, Wang Z, Zhu W, Gupta N, Skye SM, Cody DB, Levison BS, Barrington WT, Russell MW, Reed JM, Duzan A, Lang JM, Fu X, Li L, Myers AJ, Rachakonda S, DiDonato JA, Brown JM, Gogonea V, Lusis AJ, Garcia-Garcia JC, Hazen SL

(2018b) Development of a gut microbe-targeted nonlethal therapeutic to inhibit thrombosis potential. Nat Med 24:1407–1417. https://doi.org/10.1038/s41591-018-0128-1

Rothschild D, Weissbrod O, Barkan E, Kurilshikov A, Korem T, Zeevi D, Costea PI, Godneva A, Kalka IN, Bar N, Shilo S, Lador D, Vila AV, Zmora N, Pevsner-Fischer M, Israeli D, Kosower N, Malka G, Wolf BC, Avnit-Sagi T, Lotan-Pompan M, Weinberger A, Halpern Z, Carmi S, Fu J, Wijmenga C, Zhernakova A, Elinav E, Segal E (2018) Environment dominates over host genetics in shaping human gut microbiota. Nature 555:210–215. https://doi.org/10.1038/nature25973

Routy B, Le Chatelier E, Derosa L, Duong CPM, Alou MT, Daillère R, Fluckiger A, Messaoudene M, Rauber C, Roberti MP, Fidelle M, Flament C, Poirier-Colame V, Opolon P, Klein C, Iribarren K, Mondragón L, Jacquelot N, Qu B, Ferrere G, Clémenson C, Mezquita L, Masip JR, Naltet C, Brosseau S, Kaderbhai C, Richard C, Rizvi H, Levenez F, Galleron N, Quinquis B, Pons N, Ryffel B, Minard-Colin V, Gonin P, Soria J-C, Deutsch E, Loriot Y, Ghiringhelli F, Zalcman G, Goldwasser F, Escudier B, Hellmann MD, Eggermont A, Raoult D, Albiges L, Kroemer G, Zitvogel L (2018) Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. Science 359:91–97. https://doi.org/10.1126/science.aan3706

Ruiz A, Cerdó T, Jáuregui R, Pieper DH, Marcos A, Clemente A, García F, Margolles A, Ferrer M, Campoy C, Suárez A (2017) One-year calorie restriction impacts gut microbial composition but not its metabolic performance in obese adolescents. Environ Microbiol 19:1536–1551. https://doi.org/10.1111/1462-2920.13713

Schirmer M, Denson L, Vlamakis H, Franzosa EA, Thomas S, Gotman NM, Rufo P, Baker SS, Sauer C, Markowitz J, Pfefferkorn M, Oliva-Hemker M, Rosh J, Otley A, Boyle B, Mack D, Baldassano R, Keljo D, LeLeiko N, Heyman M, Griffiths A, Patel AS, Noe J, Kugathasan S, Walters T, Huttenhower C, Hyams J, Xavier RJ (2018) Compositional and temporal changes in the gut microbiome of pediatric ulcerative colitis patients are linked to disease course. Cell Host Microbe 24:600–610. https://doi.org/10.1016/j.chom.2018.09.009

Schnadower D, Tarr PI, Casper TC, Gorelick MH, Dean JM, O'Connell KJ, Mahajan P, Levine AC, Bhatt SR, Roskind CG, Powell EC, Rogers AJ, Vance C, Sapien RE, Olsen CS, Metheney M, Dickey VP, Hall-Moore C, Freedman SB (2018) Lactobacillus rhamnosus GG versus placebo for acute gastroenteritis in children. N Engl J Med 379:2002–2014. https://doi.org/10.1056/NEJMoa1802598

Schroeder BO, Birchenough GMH, Ståhlman M, Arike L, Johansson MEV, Hansson GC, Bäckhed F (2018) Bifidobacteria or fiber protects against diet-induced microbiota-mediated colonic mucus deterioration. Cell Host Microbe 23:27–40.e7. https://doi.org/10.1016/j.chom.2017.11.004

Shepherd ES, DeLoache WC, Pruss KM, Whitaker WR, Sonnenburg JL (2018) An exclusive metabolic niche enables strain engraftment in the gut microbiota. Nature 557:434–438. https://doi.org/10.1038/s41586-018-0092-4

Singh R, de Groot PF, Geerlings SE, Hodiamont CJ, Belzer C, Ten Berge IJM, de Vos WM, Bemelman FJ, Nieuwdorp M (2018a) Fecal microbiota transplantation against intestinal colonization by extended spectrum beta-lactamase producing Enterobacteriaceae: a proof of principle study. BMC Res Notes 11:190. https://doi.org/10.1186/s13104-018-3293-x

Singh V, Yeoh BS, Chassaing B, Xiao X, Saha P, Aguilera Olvera R, Lapek JD, Zhang L, Wang W-B, Hao S, Flythe MD, Gonzalez DJ, Cani PD, Conejo-Garcia JR, Xiong N, Kennett MJ, Joe B, Patterson AD, Gewirtz AT, Vijay-Kumar M (2018b) Dysregulated microbial fermentation of soluble fiber induces cholestatic liver cancer. Cell 175:679–694.e22. https://doi.org/10.1016/j.cell.2018.09.004

Smits SA, Leach J, Sonnenburg ED, Gonzalez CG, Lichtman JS, Reid G, Knight R, Manjurano A, Changalucha J, Elias JE, Dominguez-Bello MG, Sonnenburg JL (2017) Seasonal cycling in the gut microbiome of the Hadza hunter-gatherers of Tanzania. Science 357:802–806. https://doi.org/10.1126/science.aan4834

Smits LP, Kootte RS, Levin E, Prodan A, Fuentes S, Zoetendal EG, Wang Z, Levison BS, Cleophas MCP, Kemper EM, Dallinga-Thie GM, Groen AK, Joosten LAB, Netea MG, Stroes ESG, de Vos WM, Hazen SL, Nieuwdorp M (2018) Effect of vegan fecal microbiota transplantation on carnitine- and choline-derived trimethylamine-N-oxide production and vascular inflammation in patients with metabolic syndrome. J Am Heart Assoc 7:e008342. https://doi.org/10.1161/JAHA.117.008342

Sokol H, Leducq V, Aschard H, Pham H-P, Jegou S, Landman C, Cohen D, Liguori G, Bourrier A, Nion-Larmurier I, Cosnes J, Seksik P, Langella P, Skurnik D, Richard ML, Beaugerie L (2017) Fungal microbiota dysbiosis in IBD. Gut 66:1039–1048. https://doi.org/10.1136/gutjnl-2015-310746

Sonnenburg ED, Smits SA, Tikhonov M, Higginbottom SK, Wingreen NS, Sonnenburg JL (2016) Diet-induced extinctions in the gut microbiota compound over generations. Nature 529:212–215. https://doi.org/10.1038/nature16504

Spanogiannopoulos P, Bess EN, Carmody RN, Turnbaugh PJ (2016) The microbial pharmacists within us: a metagenomic view of xenobiotic metabolism. Nat Rev Microbiol 14:273–287. https://doi.org/10.1038/nrmicro.2016.17

Spinler JK, Brown A, Ross CL, Boonma P, Conner ME, Savidge TC (2016) Administration of probiotic kefir to mice with clostridium difficile infection exacerbates disease. Anaerobe 40:54–57. https://doi.org/10.1016/j.anaerobe.2016.05.008

Suez J, Zmora N, Zilberman-Schapira G, Mor U, Dori-Bachash M, Bashiardes S, Zur M, Regev-Lehavi D, Ben-Zeev Brik R, Federici S, Horn M, Cohen Y, Moor AE, Zeevi D, Korem T, Kotler E, Harmelin A, Itzkovitz S, Maharshak N, Shibolet O, Pevsner-Fischer M, Shapiro H, Sharon I, Halpern Z, Segal E, Elinav E (2018) Post-antibiotic gut mucosal microbiome reconstitution is impaired by probiotics and improved by autologous FMT. Cell 174:1406–1423.e16. https://doi.org/10.1016/j.cell.2018.08.047

Suwal S, Wu Q, Liu W, Liu Q, Sun H, Liang M, Gao J, Zhang B, Kou Y, Liu Z, Wei Y, Wang Y, Zheng K (2018) The probiotic effectiveness in preventing experimental colitis is correlated with host gut microbiota. Front Microbiol 9:2675. https://doi.org/10.3389/fmicb.2018.02675

Thaiss CA, Itav S, Rothschild D, Meijer M, Levy M, Moresi C, Dohnalová L, Braverman S, Rozin S, Malitsky S, Dori-Bachash M, Kuperman Y, Biton I, Gertler A, Harmelin A, Shapiro H, Halpern Z, Aharoni A, Segal E, Elinav E (2016) Persistent microbiome alterations modulate the rate of post-dieting weight regain. Nature 540:544–551. https://doi.org/10.1038/nature20796

Tirosh O, Conlan S, Deming C, Lee-Lin S-Q, Huang X, Barnabas BB, Bouffard GG, Brooks SY, Marfani H, Dekhtyar L, Guan X, Han J, Ho S, Legaspi R, Maduro QL, Masiello CA, McDowell JC, Montemayor C, Mullikin JC, Park M, Riebow NL, Schandler K, Scharer C, Schmidt B, Sison C, Stantripop S, Thomas JW, Thomas PJ, Vemulapalli M, Young AC, Su HC, Freeman AF, Segre JA, Kong HH, Program NCS (2018) Expanded skin virome in DOCK8-deficient patients. Nat Med. https://doi.org/10.1038/s41591-018-0211-7

van Nood E, Vrieze A, Nieuwdorp M, Fuentes S, Zoetendal EG, de Vos WM, Visser CE, Kuijper EJ, Bartelsman JFWM, Tijssen JGP, Speelman P, Dijkgraaf MGW, Keller JJ (2013) Duodenal infusion of donor feces for recurrent clostridium difficile. N Engl J Med 368:407–415. https://doi.org/10.1056/NEJMoa1205037

Vandeputte D, Kathagen G, D'hoe K, Vieira-Silva S, Valles-Colomer M, Sabino J, Wang J, Tito RY, De Commer L, Darzi Y, Vermeire S, Falony G, Raes J (2017) Quantitative microbiome profiling links gut community variation to microbial load. Nature 551:507–511. https://doi.org/10.1038/nature24460

Vangay P, Johnson AJ, Ward TL, Al-Ghalith GA, Shields-Cutler RR, Hillmann BM, Lucas SK, Beura LK, Thompson EA, Till LM, Batres R, Paw B, Pergament SL, Saenyakul P, Xiong M, Kim AD, Kim G, Masopust D, Martens EC, Angkurawaranon C, McGready R, Kashyap PC, Culhane-Pera KA, Knights D (2018) US immigration westernizes the human gut microbiome. Cell 175:962–972.e10. https://doi.org/10.1016/j.cell.2018.10.029

Vatanen T, Franzosa EA, Schwager R, Tripathi S, Arthur TD, Vehik K, Lernmark Å, Hagopian WA, Rewers MJ, She J-X, Toppari J, Ziegler A-G, Akolkar B, Krischer JP, Stewart CJ, Ajami

NJ, Petrosino JF, Gevers D, Lähdesmäki H, Vlamakis H, Huttenhower C, Xavier RJ (2018) The human gut microbiome in early-onset type 1 diabetes from the TEDDY study. Nature 562:589–594. https://doi.org/10.1038/s41586-018-0620-2

Vesty A, Biswas K, Taylor MW, Gear K, Douglas RG (2017) Evaluating the impact of DNA extraction method on the representation of human oral bacterial and fungal communities. PLoS One 12:e0169877. https://doi.org/10.1371/journal.pone.0169877

Wang H-F, Li L-F, Guo S-H, Zeng Q-Y, Ning F, Liu W-L, Zhang G (2016) Evaluation of antibody level against Fusobacterium nucleatum in the serological diagnosis of colorectal cancer. Sci Rep 6:33440

Wong SH, Kwong TNY, Chow T-C, Luk AKC, Dai RZW, Nakatsu G, Lam TYT, Zhang L, Wu JCY, Chan FKL, Ng SSM, Wong MCS, Ng SC, Wu WKK, Yu J, Sung JJY (2017) Quantitation of faecal Fusobacterium improves faecal immunochemical test in detecting advanced colorectal neoplasia. Gut 66:1441–1448. https://doi.org/10.1136/gutjnl-2016-312766

Wu GD, Compher C, Chen EZ, Smith SA, Shah RD, Bittinger K, Chehoud C, Albenberg LG, Nessel L, Gilroy E, Star J, Weljie AM, Flint HJ, Metz DC, Bennett MJ, Li H, Bushman FD, Lewis JD (2016) Comparative metabolomics in vegans and omnivores reveal constraints on diet-dependent gut microbiota metabolite production. Gut 65:63–72. https://doi.org/10.1136/gutjnl-2014-308209

Wu H, Esteve E, Tremaroli V, Khan MT, Caesar R, Mannerås-Holm L, Ståhlman M, Olsson LM, Serino M, Planas-Fèlix M, Xifra G, Mercader JM, Torrents D, Burcelin R, Ricart W, Perkins R, Fernàndez-Real JM, Bäckhed F (2017) Metformin alters the gut microbiome of individuals with treatment-naive type 2 diabetes, contributing to the therapeutic effects of the drug. Nat Med 23:850–858. https://doi.org/10.1038/nm.4345

Yang J-Y, Kim M-S, Kim E, Cheon JH, Lee Y-S, Kim Y, Lee S-H, Seo S-U, Shin S-H, Choi SS, Kim B, Chang S-Y, Ko H-J, Bae J-W, Kweon M-N (2016) Enteric viruses ameliorate gut inflammation via toll-like receptor 3 and toll-like receptor 7-mediated interferon-β production. Immunity 44:889–900. https://doi.org/10.1016/j.immuni.2016.03.009

Yu J, Feng Q, Wong SH, Zhang D, Liang QY, Qin Y, Tang L, Zhao H, Stenvang J, Li Y, Wang X, Xu X, Chen N, Wu WKK, Al-Aama J, Nielsen HJ, Kiilerich P, Jensen BAH, Yau TO, Lan Z, Jia H, Li J, Xiao L, Lam TYT, Ng SC, Cheng AS-L, Wong VW-S, Chan FKL, Xu X, Yang H, Madsen L, Datz C, Tilg H, Wang J, Brünner N, Kristiansen K, Arumugam M, Sung JJ-Y, Wang J (2017) Metagenomic analysis of faecal microbiome as a tool towards targeted non-invasive biomarkers for colorectal cancer. Gut 66:70–78. https://doi.org/10.1136/gutjnl-2015-309800

Zeevi D, Korem T, Zmora N, Israeli D, Rothschild D, Weinberger A, Ben-Yacov O, Lador D, Avnit-Sagi T, Lotan-Pompan M, Suez J, Mahdi JA, Matot E, Malka G, Kosower N, Rein M, Zilberman-Schapira G, Dohnalova L, Pevsner-Fischer M, Bikovsky R, Halpern Z, Elinav E, Segal E (2015) Personalized nutrition by prediction of glycemic responses. Cell 163:1079–1094. https://doi.org/10.1016/j.cell.2015.11.001

Zhang C, Derrien M, Levenez F, Brazeilles R, Ballal SA, Kim J, Degivry M-C, Quéré G, Garault P, van Hylckama Vlieg JET, Garrett WS, Doré J, Veiga P (2016) Ecological robustness of the gut microbiota in response to ingestion of transient food-borne microbes. ISME J 10:2235–2245. https://doi.org/10.1038/ismej.2016.13

Zhao L, Zhang F, Ding X, Wu G, Lam YY, Wang X, Fu H, Xue X, Lu C, Ma J, Yu L, Xu C, Ren Z, Xu Y, Xu S, Shen H, Zhu X, Shi Y, Shen Q, Dong W, Liu R, Ling Y, Zeng Y, Wang X, Zhang Q, Wang J, Wang L, Wu Y, Zeng B, Wei H, Zhang M, Peng Y, Zhang C (2018) Gut bacteria selectively promoted by dietary fibers alleviate type 2 diabetes. Science 359:1151–1156. https://doi.org/10.1126/science.aao5774

Zheng JH, Nguyen VH, Jiang S-N, Park S-H, Tan W, Hong SH, Shin MG, Chung I-J, Hong Y, Bom H-S, Choy HE, Lee SE, Rhee JH, Min J-J (2017) Two-step enhanced cancer immunotherapy with engineered Salmonella typhimurium secreting heterologous flagellin. Sci Transl Med 9:9537. https://doi.org/10.1126/scitranslmed.aak9537

Zmora N, Zilberman-Schapira G, Suez J, Mor U, Dori-Bachash M, Bashiardes S, Kotler E, Zur M, Regev-Lehavi D, Brik RB-Z, Federici S, Cohen Y, Linevsky R, Rothschild D, Moor AE,

Ben-Moshe S, Harmelin A, Itzkovitz S, Maharshak N, Shibolet O, Shapiro H, Pevsner-Fischer-M, Sharon I, Halpern Z, Segal E, Elinav E (2018) Personalized gut mucosal colonization resistance to empiric probiotics is associated with unique host and microbiome features. Cell 174:1388–1405.e21. https://doi.org/10.1016/j.cell.2018.08.041

Zou J, Chassaing B, Singh V, Pellizzon M, Ricci M, Fythe MD, Kumar MV, Gewirtz AT (2018) Fiber-mediated nourishment of gut microbiota protects against diet-induced obesity by restoring IL-22-mediated colonic health. Cell Host Microbe 23:41–53.e4. https://doi.org/10.1016/j.chom.2017.11.003

Zuo T, Wong SH, Lam K, Lui R, Cheung K, Tang W, Ching JYL, Chan PKS, Chan MCW, Wu JCY, Chan FKL, Yu J, Sung JJY, Ng SC (2018) Bacteriophage transfer during faecal microbiota transplantation in Clostridium difficile infection is associated with treatment outcome. Gut 67:634–643. https://doi.org/10.1136/gutjnl-2017-313952