Computational and Structural Biotechnology Journal 20 (2022) 615–627

COMPUTATIONAL AND STRUCTURAL BIOTECHNOLOGY JOURNAL

journal homepage: www.elsevier.com/locate/csbj

Mini review

The emerging potential of microbiome transplantation on human health interventions

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ARTICLE INFO

Article history:
Received 5 October 2021
Received in revised form 6 January 2022
Accepted 8 January 2022
Available online 19 January 2022

Keywords:
Microbiome transplantation
Microbiota
Dysbiosis

ABSTRACT

The human microbiome has been the subject of intense research over the past few decades, in particular as a promising area for new clinical interventions. The microbiota colonizing the different body surfaces are of benefit for multiple physiological and metabolic processes of the human host and increasing evidence suggests an association between disturbances in the composition and functionality of the microbiota and several pathological conditions. This has provided a rationale for beneficial modulation of the microbiome. One approach being explored for modulating the microbiota in diseased individuals is transferring microbiota or microbiota constituents from healthy donors via microbiome transplantation. The great success of fecal microbiome transplantation for the treatment of *Clostridioides difficile* infections has encouraged the application of this procedure for the treatment of other diseases such as vaginal disorders via transplantation of vaginal microbiota, or of skin pathologies via the transplantation of skin microbiota. Microbiome modulation could even become a novel strategy for improving the efficacy of cancer therapies. This review discusses the principle, advantages and limitations of microbiome transplantation as well as different clinical contexts where microbiome transplantation has been applied.

Contents

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https://doi.org/10.1016/j.csbj.2022.01.009

1. Introduction

The human body is colonized by complex communities of microorganisms including bacteria, archaea and fungi that collectively constitute the "microbiota" and the collection of their genes constitutes the "microbiome" [1]. These microbial communities interact closely with the host to modulate almost any aspect of the host physiological functions ranging from food digestion to immune homeostasis. Various pathological disorders, including among others inflammatory bowel disease (IBD) [2], allergies [3], obesity [4] and cardiovascular disease [5], have been linked to an imbalance of the microbiota, generally referred as dysbiosis (Fig. 1). Hence, a major focus of current research is the therapeutic potential of manipulating the microbiome to improve human health. Among the different procedures explored for this purpose, microbiome transplantation, which is the process of transferring the microbiome of a healthy donor to a diseased recipient individual, represents a promising approach (Fig. 2). Most clinical evidence of the efficacy of microbiome transplantation for the treatment of pathological disorders has been obtained with fecal microbiota transplantation (FMT), which consists in the administration of prepared stool material from a healthy donor to a diseased individual [6]. Although the use of fecal transfer from healthy individuals to treat gastrointestinal diseases dates back to the 4th century [7], this procedure has experienced a particularly fast development during the last decade [6,8]. Clinical studies, including randomized controlled trials, have proven the effectiveness of FMT to treat recurrent *Clostridioides difficile* infection (rCDI), with cure rates higher than 85% [9,10]. The small percentage of rCDI cases where FMT failed to confer benefit seems to be associated with patient attributes such as prior hospitalization, procedural features and the severity of the infection [11]. Promising findings from several studies have also denoted the practicality of FMT for the treatment of ulcerative colitis [12,13], Crohn's disease [14], chronic pouchitis [15], metabolic diseases [16] as well as neurological disorders [17]. Beyond FMT, the spectrum of microbiome transplantation has been extended to the skin [18] and vaginal microbiome [19] for the treatment of disorders related to these body sites.

A key issue in microbiome transplantation research is to define the microbiome components that provide benefit. This information will facilitate the development of therapeutic approaches based on artificial combinations of these components. Recent advances in omics technologies, high-throughput sequencing and bioinformatic tools have advanced our understanding of the human microbiome composition and function [20–22]. Microbiomes have been characterized in different parts of the body and in cohorts of healthy individuals representing different age, gender and lifestyles, allowing to gain more precise information on environmental and genetic factors influencing microbiome composition and diversity [23–25]. Comparisons of microbiomes from healthy and diseased individuals has allowed the identification of community members or community functions enriched or depleted that may be potentially associated with the disease [26,27]. As examples, a dysbiosis associated with colorectal cancer is usually characterized by an increased prevalence of members of the genera *Fusobacterium, Porphyromonas*, and *Peptostreptococcus* among others [28], whereas individuals suffering from type 2 diabetes show a reduction in the butyrate-producing potential [29]. However, the factors driving the shifts in the microbiome structure and function during dysbiosis are in most cases unknown and, therefore, a causal contribution of microbiome dysbiosis for specific pathological disorders has been difficult to establish.

Despite the promising therapeutic potential of microbiome transplantation, the mechanisms underlying the benefit of the engrafted microbiota remains poorly characterized as well as the factors responsible for the high inter-individual variation in the engraftment of donor strains. A better understanding of microbial interactions and functions of community members and their influence in host health and disease will allow in the future to transfer

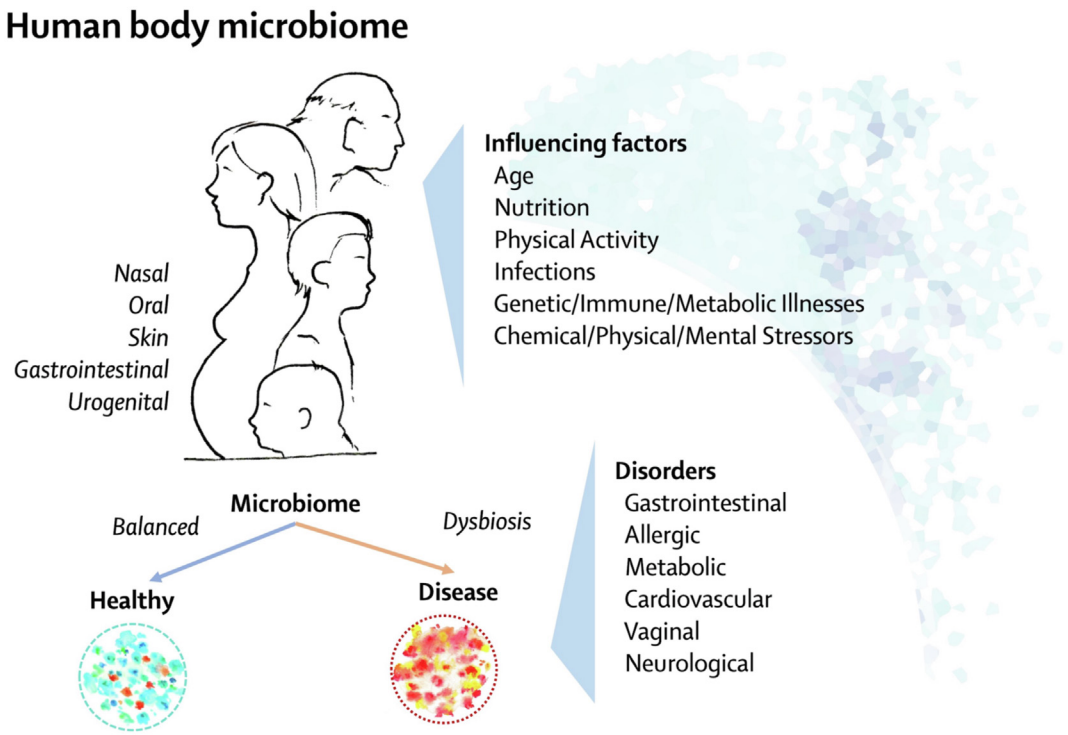


Fig. 1. Schematic representation of the human microbiome, factors influencing the microbiome composition and disorders associated with dysbiosis. Illustration by Victoria Junca.

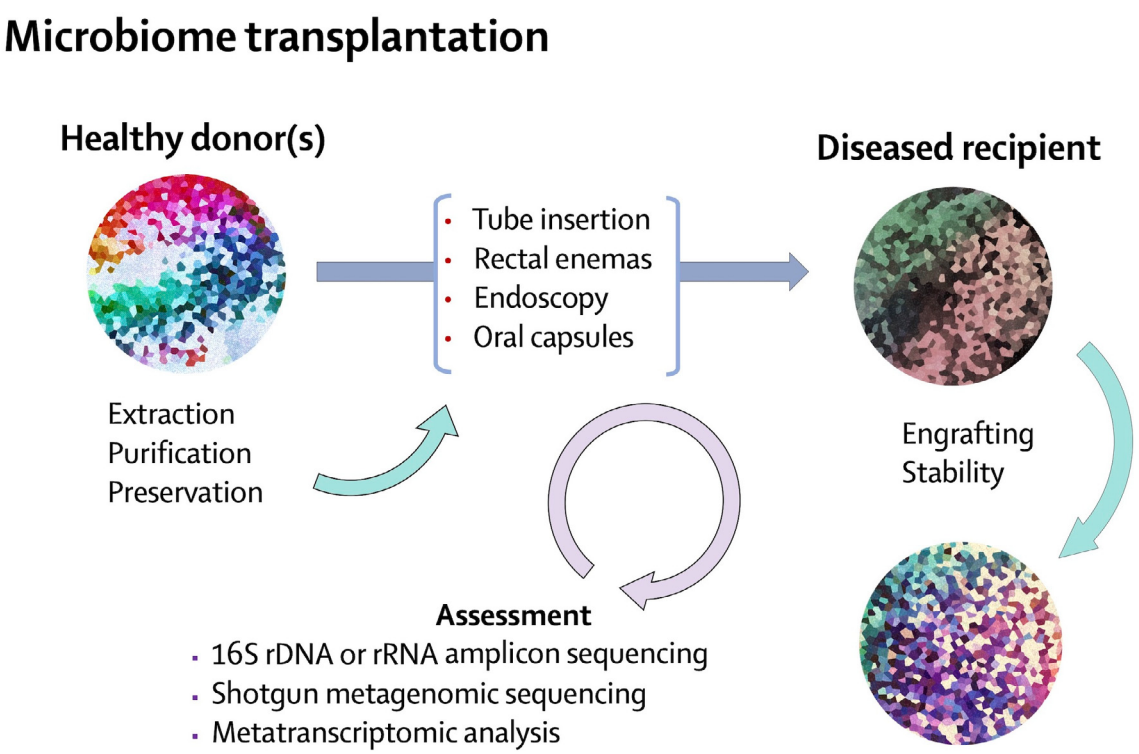


Fig. 2. Schematic representation of the human microbiome transplantation, the different methods used to transfer the microbiome from donors into recipients as well as the methods used for assessing the microbiome composition and engraftment efficiency.

defined microbiota rather than undefined community mixes which also may comprise unwanted functions.

2. Dysbiosis and microbiota

Dysbiosis can be described as an alteration of the community structure of the host microbiota associated with disease. It can involve loss of beneficial commensals microorganisms, an expansion of potentially harmful microbes (the so-called pathobiome, which considers not only the potentially harmful microorganisms themselves but also the complex interactions between microbes and the environment that may trigger disease), and/or a loss of microbial diversity [30–32]. Several human pathological conditions previously considered of unknown etiology (idiopathic) such as obesity, diabetes, Parkinson's disease or arthritis have been the focus of microbiome studies. One of the major aimsi of these studies has been to determine the possible links between bacterial composition, abundance and activities, either as causal agents or as protective, and the initiation or progression of disease [33]. However, there is still no clear agreement on what constitutes a healthy microbiome and discrimination between commensals, pathobionts and opportunistic pathogens is more complex than previously thought. Rath *et al.* [34] recently introduced the concept of "pathofunction", which are specific functional features of the microbiota such as production of detrimental metabolites, extracellular enzymes, or immunostimulatory molecules that have the potential to cause disease, whereas other functions such as the formation of short chain fatty acids are typically correlated with a healthy microbiome. Some of these detrimental bacterial metabolites are trimethylamine, secondary bile acids, hydrogen sulfide, indole/phenol/p-cresol, N-nitrosamine, branched-chain amino acids, 4-ethylphenylsulfate and uric acid [34]. An excess of these microbiota-related compounds can induce host damage directly or indirectly by affecting downstream processes. For example, trimethylamine, a compound produced by the microbiota from dietary quaternary amines, has been associated with an increased risk for cardiovascular diseases [35]. The production of these compounds is not restricted to specific bacterial groups but rather involve a diverse range of taxonomically distinct microorganisms [34], indicating functional redundancy of taxonomically distinct bacteria [36]. Therefore, a better understanding of the pathofunctions and the carrying bacteria, their interaction with the host as well as with the other members of the microbiota, will enable to design intervention approaches to reduce pathofunctions and improve host health. These strategies can involve targeting the pathofunction carrying bacteria, blocking the activity of pathofunctions or stimulating commensals that compete for growth substrates with pathofunction carriers.

Interestingly, there is evidence showing that the gut microbiome can exert remote effects in systems beyond the intestine and the interaction within the microbiota-gut-brain axis has become an intensive focus of research in recent years [37]. In this regard, microbiome derived short-chain fatty acids, secondary bile acids, and tryptophan metabolites have been shown to have a modulating effect on the central nervous system activity [38]. The microbiome can also be a source of neuroactive metabolites such as γ-aminobutyric acid, norepinephrine, and dopamine [39]. Increasing numbers of studies have reported a link between gut microbiota dysbiosis and neurological disorders such as multiple sclerosis [40], autism [41], depression [42] and Parkinson's disease [43]. The gut microbiome is also a major regulator of circulating estrogens in women and reduction of estrogens resulting from dysbiosis of the gut microbiota can lead to several pathological disorders such as endometrial hyperplasia, endometriosis and infertility [44].

The gut microbiota is also critical for the development and modulation of the mucosal innate and adaptive immune system and exerts an important role in protecting against pathogens by maintaining gut integrity and regulating intestinal barrier perme-

ability [45]. Dysbiosis of the gut microbiome can result in alterations of the immune system that can lead to systemic dissemination of commensal microorganism and increased susceptibility to pathogenic invasion.

3. Microbiome transplantation: Benefits and limitations

Microbiome transplantation has been investigated for the treatment of several pathological disorders including *Clostridioides difficile* infections [46], ulcerative colitis [47], Crohn's disease [48], cancer [49] as well as in skin [18] and vaginal [50] pathologies (described in more detail in the following sections). Despite its promising potential, this approach also has some limitations. For example, there is substantial interindividual variability on the microbiota that makes it difficult to clearly differentiate healthy from dysbiotic microbiota and to ascertain a causal relationship between altered microbiota and disease [51,52]. To establish a direct contribution of a dysbiotic microbiota to a pathological condition, microbiota-devoid germ-free mice transplanted with human microbiota from individuals with and without disease have been used in several studies [53–55]. Also conventional mice treated with broad-spectrum antibiotics to deplete the recipient microbiota have been used to establish a causal role of microbiome alterations in human diseases [56,57]. Although murine models have been useful for establishing links between altered microbiota and disease, they have several limitations that hinder the direct translatability into the human system since not all members of the human microbiota are capable of efficiently colonizing the murine system [58]. It is also important to note that extrinsic factors such as diet or lifestyle that can drive microbiome dysbiosis cannot be reflected in mouse models [58].

An additional problem is that the human microbiome comprises not only communities of bacteria but also archaea, fungi and viruses that alone or in concert with formed metabolites could play a role in disease. This poses a challenge for the identification of the causal microbiome components responsible for the disease.

The efficacy of microbiome engraftment and long-term establishment is also highly variable among recipient individuals [59,60]. Hence, efforts need to be made to achieve a better understanding of the mechanisms governing the microbiome assembly and function after transplantation in order to identify microbiome features in the recipient and donor that predict efficacy. This can help to select appropriate donor-recipient combinations and will enable the application of microbiome transplantation in a personalized fashion.

Finally, there is a lack of standardization regarding routes of administration, timing, dosing and safety rules that makes the interpretation and comparison of data across multiple studies difficult.

4. Tracking bacterial engraftment after microbiome transplantation

In patients undergoing microbiome transplantation, samples are collected before and after the treatment to retrieve information on the efficacy of donor bacterial strains engraftment and stability (Fig. 2). This information enables to correlate changes in the microbiome composition with the success or failure of the treatment. The most common approach used for assessing the composition of the donor bacterial community and for following the establishment and stability of the transplanted microbiome is 16S rRNA gene amplicon sequencing [61]. Typically, a fragment of the 16S rRNA gene as taxonomic marker is amplified allowing to deduce the composition of the amplicon mixture as an indication for the taxonomic composition [61]. Although this method is usually fast and cost-efficient, it does not allow to evaluate the presence of crucial functions and also it is not possible to differentiate between active (or viable) and inactive (dead lysed or degraded) community members. Due to the short life span of extracellular RNA compared with DNA, sequence libraries constructed from reverse transcripts of RNA have been reported to be a more suitable method for identifying the active components of a bacterial community [62]. Although there are some programs available that enable to deduce functional diversity based on 16S rDNA or rRNA profiles [63,64], one should be cautious when using these programs as important functions are often not encoded in the core genome of a given species or genus. While shotgun metagenomic sequencing, consisting in the random sequencing of DNA of a given sample, has emerged as an alternative to amplicon sequencing [65], sequencing costs are significantly exceeding those of amplicon sequencing. However, metagenomic analysis does not allow the identification of microbiome functions that can be of crucial importance under a given condition. In this regard, metatranscriptomic analysis, which involves the massive sequencing of mRNA extracted from an ecosystem, would give information on active community members and active metabolic functions [66]. Metatranscriptomic analysis is less frequently applied in microbiome research, mainly due to the high instability of mRNA as well as the requirement of additional methodological efforts such as the depletion of 16S rRNA.

There are many factors that may influence the inferred microbiome composition of a given sample, and would impact the assessment of the microbiome transplantation success or the changes of the community composition. Among them are the experimental procedures for collecting, preserving and extracting DNA from the samples [67–69]. Identifying and controlling for contaminant bacterial DNA in the reagents used for these procedures is crucial, specifically for low-bacterial biomass environments [70]. In case of metagenomic shotgun sequencing, a reasonable percentage of bacterial compared to host DNA is indispensable to characterize the bacterial metagenome at affordable cost [71].

In amplicon sequencing, the selection of the hypervariable region of the 16S rRNA gene targeted or the specific primer variant used for amplification are of crucial importance. For example, whereas primers targeting the V1-V2 hypervariable regions have now been optimized to detect Bifidobacteriaceae, primers targeting the V4 region still fail to detect *Cutibacterium* sp. [36]. Furthermore, different regions display different efficiency for discriminating between different bacterial taxa [72]. An additional key issue is the sequencing technology applied and the tools used for bioinformatic handling of the data. Most of the short-read sequencing methods rely on Illumina sequencing, which yield millions to billions of high-quality sequence reads of a length of typically up to 300 basepairs. However, a disadvantage of this technology is the impossibility to assembly long sequences, specifically when sequence repeats are located in the target sequence. Thus, long-read sequencing technologies such as the single-molecule real-time sequencing developed by Pacific Biosciences or the more affordable Nanopore sequencing are necessary to retrieve high-quality metagenome-assembled genomes [73].

Several pipelines and programs are available to analyze amplicon sequencing data. DADA2, a software package that models and corrects Illumina-sequenced amplicon errors [74], infers exact amplicon sequence variants from high-throughput sequencing data and avoids the less accurate clustering of sequences into taxonomic units. The naïve Bayesian classifier provided by the Ribosomal Database Project (RDP) is one of the most widely used tools for taxonomic classification of 16S rRNA sequences [75]. This tool allows down to genus level assignments as well as species-level assignments to 16S rRNA gene fragments by exact matching. The SILVA database (https://www.arb-silva.de) is also a highly valuable source of information [76]. These databases require continuous

update, specifically when considering the permanent flow of new information in bacterial taxonomy.

Further analysis of amplicon data requires statistical analysis. A recent review article [77] focused on the analysis of human microbiome studies revealed that there is still a significant fraction of manuscripts where the software used for the analysis is not mentioned or even are not applying any statistical analysis on the data obtained. That review [77] also gives a systematic overview of major data analysis strategies.

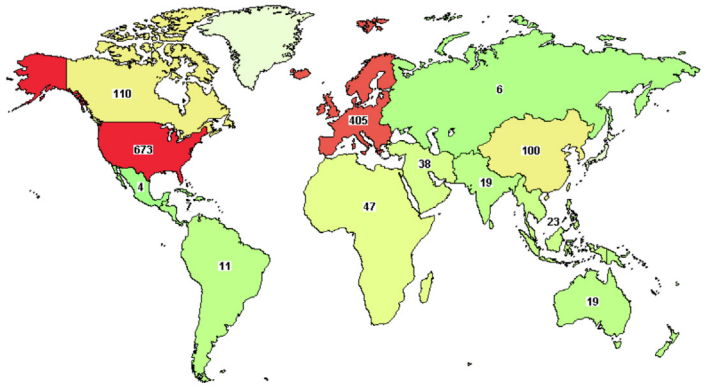
The biological interpretation of metagenomic information requires sophisticated computational analyses and comprises read assembly, binning and taxonomic profiling. A large set of bioinformatic tools is available for practically each step. To help in evaluating these tools, the Critical Assessment of Metagenome Interpretation (CAMI) initiative was created, which aims to evaluate computational methods for metagenome analysis, and the performance of various metagenome assembly, binning and taxonomic profiling programs has been assessed [78]. Sequences are typically annotated by computational analysis using public databases. However, due to the rapid advances in sequencing technologies and increasing amounts of sequence information, the level of misannotations in public databases is immense [79,80]. It is thus advisable for the future to build up curated databases for specific research questions of microbial communities in various diseases [26,36].

5. Fecal microbiome transplantation

FMT involves the transfer of complex bacterial communities extracted from healthy donors to diseased individuals in order to change the microbiome composition and correct dysbiosis [6]. The microbiome content can be delivered into the recipient by tube insertion, rectal enemas, endoscopy or oral capsules, via the upper or lower gastrointestinal tract [81]. In fact, FMT via capsules makes the treatment more accessible than delivery through other routes and enables the treatment of patients that cannot tolerate endoscopic procedures. A systematic review of studies using encapsulated FMT to treat rCDI showed similar cure rates evidencing that this method is as effective as delivering FMT through other routes [81]. It is also documented that capsules can be stored for months frozen without loss of activity and the use of appropriate coating material ensures passing the stomach and release of the active content in the intestine [82]. Furthermore, capsules can be even stored in the patient's own refrigerator [83].

FMT has been shown to be highly effective for the treatment of rCDI [9,10], a disease that is poorly treatable with conventional antibiotic therapy, with a treatment success rate of 85%-89,7% [84]. The efficacy of FMT for treatment of rCDI has increased the interest in its application for other pathological disorders, leading to a number of registered clinical trials (Fig. 3). Overall, there is now accumulating evidence that FMT can induce remission in ulcerative colitis [12,13], however, with success rates below those observed in rCDI. The results of a first clinical trial for the treatment of Crohn's disease, the second major subtype of inflammatory bowel disease, are also promising [14] as were those analyzing the effect of healthy microbiota transfer in chronic pouchitis [15]. Microbiota transplantation is currently being tested in the context of several other diseases, with a recent overview given by Goldenberg and Merrick [12].

Of particular importance in FMT is the selection of stool donors, which should be chosen based on their good health condition and absence of any detectable infectious agents [85]. In 2019, two immunocompromised patients were reported to develop bacteremia caused by extended-spectrum beta-lactamase-producing *Escherichia coli* after FMT in two independent clinical trials after receiving FMT from the same donor [86]. Screening for these pathogens was made standard practice since then [87]. However, it should also be noted that microbial phenotypes may be transmitted during FMT that can promote later development of non-communicable disorders in the recipient. In fact, centralized stool banks that organize recruitment and screening the health status of the donors including health questionnaires as well as stool and blood testing are currently being established or discussed [87]. History of malignancies or autoimmune disease as well as abnormal blood values, serology for Hepatitis virus and Human immunodeficiency virus are excluding criteria [88]. Screening donor stool for potential pathogens is an important issue in FMT and constitutes a strict criterion for donor selection [89]. Stool testing not only includes common enteric pathogens such us *C. difficile* or *Helicobacter pylori* but also antibiotic-resistant bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant Enterococci (VRE), extended-spectrum β-lactamase-producing Enterobacteriaceae, and carbapenem-resistant Enterobacteriaceae [88]. Donor stools are also screened for viruses such as norovirus, rotavirus and adenovirus, parasites such as *Giardia lamblia* and *Cryptosporidium* spp. and protozoa/helminths such as



Conditions	Number of studies
Gastrointestinal disorders	267
Infections	232
Metabolic Diseases	172
Body Weight	135
Glucose Metabolism Disorders	125
Immune System Diseases	121
Colonic Diseases	111
Skin Diseases	96
Inflammatory Bowel Diseases	92
Respiratory Tract Diseases	86
Endocrine System disorders	80
Nutrition Disorders	76
Hypersensitivity	70
Mental Diseases	67

Fig. 3. Number of selected registered clinical trials on microbiome transplantation per country at September 2021 (Source https://clinicaltrials.gov/). Included are the trials under categories: recruiting, not yet recruiting, active, but not recruiting, completed, enrolling by invitation, terminated studies, interventional Sstudies). Non-redundant categories selected showing the main target ofmicrobiome effect/intervention being studied.

Blastocystis hominis and *Dientamoeba fragilis* [88]. Due to the current Covid-19 pandemic, inclusion of a test for SARS-CoV-2 via nasopharyngeal swab and/or RNA detection in stool has been recommended [90]. Thus, the identification of healthy donors that meet all criteria for FMT is not always easy and this screen often results in the exclusion of a high percentage of potential donors [89].

Differences in FMT efficacy have been observed between different diseases and may reflect differences regarding the importance of the gut microbiota in their respective pathogenesis. For example, whereas a rCDI is almost purely caused by alterations in the gut microbiota, other diseases are much more complex and involve immune and genetic factors [91]. FMT studies on IBD patients have revealed variations in the recipient responses depending on the donor stool used, which indicate differences in the capacity of donor stools to engraft the recipient. A successful engraftment is typically manifested by a change of the microbial community composition of the recipient to one resembling the donor and by an increase in microbial diversity. Hence, selection of appropriate stool donors based on their microbiota composition is key for FMT success [92]. Typically, the microbiota composition of diseased individuals, *e.g.* in ulcerative colitis [93], exhibits reduced diversity compared to healthy microbiota and a high microbial diversity of the donor stool has been reported as crucial for treatment success [94,95]. In addition, FMT should also restore the specific metabolic disturbances associated with the given disease phenotype such as the depletion of butyrate-producing bacterial species in Crohn's disease and ulcerative colitis [96]. In these cases, only microorganisms associated with the specific metabolic pathway will be of benefit for the patient. It has been suggested that treatment success could be improved by using a multi-donor approach [97]. Also the term "super-donor" has been proposed to describe donors the stool of which yield significantly better FMT outcomes than the stools of other donors [98]. Following FMT, the recipient microbiota has been shown to contain species derived from the recipient- and those derived from the donor as well as newly acquired species [60], suggesting that complex microbial interactions contribute to FMT engraftment. Overall, the stability of the changes introduced by FMT in recipients can range from several days to several years [99,100]. To improve engraftment, an intensified protocol comprising a higher frequency of FMT over an extended time period was suggested [101].

In addition to the donor, also characteristics related to the recipient can have a significant effect on the engraftment success and on the stability of the transplanted microbiota. One important factor is host genetics, which has been shown to influence the composition of the gut microbiome [102]. More recently, an association between specific human gene variants and the abundance of specific microbial taxa such as *Rikenellaceae*, *Faecalibacterium*, *Lachnospira* and *Eubacterium* in the gut microbiota has been identified that can also explain differences in engraftment success in different recipients [103]. Also differences in the recipient immune response toward the transplanted microbiota has been shown to influence the FMT success [92]. Accordingly, an immune screening approach was suggested for selecting the most compatible gut microbiota donor for ulcerative colitis patients before FMT [104]. More recently, however, it was shown that the suggested immunologic compatibility testing was not useful for donor selection [105]. The clinical status of the recipient and taken medications as well as dietary interventions are also important factors to consider when discussing the success of FMT.

In addition to bacteria, fungi, archaea and viruses play a role in the establishment of the novel commensal community after FMT and in the therapeutic effects. However, compared to reports on the microbiota, reports on the mycobiome, the archaeome and the virome are scarce. The existing literature on the human mycobiota and how fungi interact with the human host and other microbes has recently been reviewed [106]. Analysis of the mycobiome performed in IBD [107] and colorectal cancer [108] patients showed a higher Basidiomycota/Ascomycota ratio and a decreased proportion of Saccharomycetes in both cases in comparison to healthy individuals. These observations suggest that the mycobiome might play a role in both diseases. A high abundance of *Candida* in the recipient stool has been associated with a high clinical response to FMT in a cohort of ulcerative colitis patients [109]. Clearly, further studies are required to better evaluate the effects of the mycobiome in FMT.

Safety is an important issue in FMT, particularly when the recipients are immunocompromised patients. As transfer of undefined microbial communities may pose some risks, it has been investigated whether a sterile filtrate of fecal microbiota also exerts beneficial biological effects. In a small cohort of five patients with rCDI, it was shown that such a filtrate was sufficient to change the gastrointestinal microbiota and eliminate symptoms [110]. This indicates that bacterial components, metabolites, or bacteriophages could mediate the effects of the classical transfer of whole fecal microbiota. Significant efforts are currently being made to characterize the human virome and the effects exerted by fecal virome transplantation (for a review see [111]). Several reports on fecal transfer in rCDI have emphasized the importance of the viral components. Thus, whereas Zuo *et al.* [112] reported that CDI patients exhibited a high abundance but low diversity of Caudovirales that significantly decreased after FMT, Fujimoto *et al.* [113] revealed that the proportion of Microviridae increased after FMT in CDI recipients. Studies reported by Park *et al.* [114] indicated that bacteriophage abundance in stool donors may have some role in determining the relative success of FMT, with a low bacteriophage number but high diversity increasing success rate. Also data from IBD patients support the importance of virome alteration [115]. Similar to CDI patients, patients with ulcerative colitis exhibited an increased abundance of Caudovirales [116]. However, Caudovirales were even more significantly enriched in individuals who failed to respond to a fecal transplant [116]. Given the importance of the virome in fecal transplantation, further studies are needed to better define the effects of the different components.

6. Skin microbiome transplantation

The skin is a large organ harboring a high diversity of commensal microorganisms that exert barrier functions and maintain homeostasis [117]. The bacterial taxa associated with the skin microbiome vary depending on the features of the skin sites which can be differentiated as sebaceous, moist and dry. For example, whereas *Cutibacterium* species are prevalent at sebaceous skin areas, *Staphylococcus* and *Corynebacterium* spp. are more abundant in moist environments [117]. The skin microbiota plays a pivotal role protecting against pathogenic microorganisms by competition in a process named 'colonization resistance' or by producing antimicrobial peptides [117,118].

Many common skin disorders such as acne and atopic dermatitis are associated with dysbiosis of skin microbiota [119,120]. Similar to FMT, skin microbiota transplantation could provide a suitable approach for the amelioration of skin diseases severity. However, research on skin microbiota transplantation is still in its infancy. Skin microbiome transplantation can be achieved by transferring either whole skin microbiota collected from a healthy individual or an artificial mixture of selected microorganisms to the recipient skin area [121]. Major work so far has been invested in the treatment of atopic dermatitis (AD), which is characterized by a high abundance of *Staphylococcus aureus* and a decreased microbial diversity [122]. Generally, treatment of AD flares with

emollients is reported to restore the diversity of the skin microbiome and reduce disease severity [123]. As metabolic products of *Staphylococcus epidermidis* were reported to improve skin moisture retention, Nodake *et al.* [124] determined the effect of application of *S. epidermidis* and could show that this treatment increased the lipid content of the skin and suppressed water evaporation. More importantly, coagulase-negative staphylococci (CoNS) are able to produce various types of bacteriocins and small cyclic peptides which inhibit the *S. aureus* quorum-sensing system [125]. As CoNS strains with antimicrobial activity were common in the normal population but rare in AD patients, it was thought that such strains may be good agents for the treatment of AD [118]. Furthermore, the observation that application of antimicrobial CoNS strains to the skin of AD patients resulted in decreased colonization by *S. aureus* [118], fostered the implementation of a clinical trial where *Staphylococcus hominis* A9, a bacterium isolated from healthy human skin, was tested as a topical therapy for AD [126]. In fact, the safety and potential benefits of such bacteriotherapy could be demonstrated in those clinical studies.

The skin microbiota has recently been reported as the main reservoir of *Roseomonas mucosa*, which was classified as an emerging opportunistic pathogen [127]. Interestingly, *R. mucosa* collected from healthy volunteers improved the outcomes of AD in experimental models through multiple mechanisms that target epithelial barrier function, innate/adaptive immune balance and *S. aureus* growth. On the other hand, isolates of *R. mucosa* from patients with AD were found to worsen the disease outcomes in these models [128]. Based on these pre-clinical data, the therapeutic potential of topical *R. mucosa* has been tested in a small cohort of AD patients [18]. Although treatment was associated with a significant clinical improvement, a direct role of *R. mucosa* in AD could not be established since the composition of the skin microbiota before and after treatment with *R. mucosa* was not determined in the enrolled patients [18].

Imbalance in skin microbiota and specifically the presence of inflammatory *C. acnes* strains has been associated with the development of acne [129]. In this context, application of non-acne-causing *C. acnes* strains to the skin was proposed as a potential therapy. Accordingly, the modulation of the skin microbiome after transfer of either complete microbiomes or solutions containing distinct *C. acnes* strains was investigated [130]. The authors demonstrated some engraftment after application of the complete microbiomes and the establishment of *C. acnes* strains when applied as multi-strain mixture [130]. Clinical improvements have been also observed in a small pilot study after application of *C. acnes* formulations to patients [129].

Skin microbiome transplantation has also been considered as a means to remove bad armpit odor [131], where the malodor-causing microbes are replaced by non-odorous microorganisms such as *S. epidermidis* or *C. acnes* [132]. Although this strategy is looking promising, more investigation is required to determine the stability, efficacy, and safety of skin microbiota manipulations in general.

7. Vaginal microbiome transplantation

The vagina harbors high numbers of commensal microorganisms. Although *Lactobacillus* spp. have been identified as dominant microorganisms of vaginal microbiota of healthy reproductive-age women [133], the composition is deeply influenced by physiological factors such as hormone levels as well as other factors such as sexual activity [134–137]. By producing lactic acid, *Lactobacilli* sustain a low pH in the vaginal environment that inhibit growth of potential pathogens [135]. Vaginal dysbiosis has been associated with several pathological conditions such as bacterial vaginosis, increased risk for sexual transmitted infections, preterm labor or preterm premature rupture of membrane [138,139]. For example, bacterial vaginosis, a very common condition affecting women of reproductive age [140], is caused by a decline in the number of *Lactobacillus* and overgrowth of anaerobic bacteria such as *Gardnerella*, *Prevotella, Atopobium* or *Fannyhessea* [141,142]. Although conventional treatment of bacterial vaginosis with oral or topical antibiotics may show temporary efficacy, recurrence of infection is frequently observed [143]. Clinical studies to investigate the efficacy of oral or vaginal administration of *Lactobacillus* spp. either alone or as adjunct therapy to patients suffering of bacterial vaginosis have been performed [144,145]. In these studies, a large set of *Lactobacillaceae* species have been used, including *Lacticaseibacillus casei* or *rhamnosus, Levilactobacillus brevis*, *Limosilactobacillus reuteri* or *Lactiplantibacillus plantarum*, which are rarely present in vaginal samples. Vaginal communities are typically dominated by *Lactobacillus crispatus* or *Lactobacillus iners* and more infrequently by *Lactobacillus jensen*ii or *Lactobacillus gasseri* [133]. Whereas *L. iners* is generally excluded because it may encode factors that are harmful to the vaginal mucosa [146], a mixture of *L. crispatus, L. gasseri, L. jensenii* and *L. rhamnosus* is often applied [147].

The outcome of the studies investigating the effect of probiotics administration for the treatment of vaginal disorders is highly controversial. For example, two recent case studies not only failed to demonstrate an increase in cure rate after treatment but they also showed that the applied *L. rhamnosus* and *L. reuteri* strains did not change the community structure or could establish themselves in the targeted ecosystem [144,145]. A recent systematic review [148] indicated that probiotics are promising tools to cure vaginosis, however, the authors also indicated that the applied bacterial strains failed to colonize the vagina and could not be detected after the dosing period. To improve probiotic delivery and establishment into the vagina, new methods such as incorporation of probiotics in fibers to optimize survival [149] or of 3D printed scaffolds embedded with bacteria [143] have been proposed.

Due to the success of FMT to treat *C. difficile* infections, vaginal microbiome transfer (VMT) is currently discussed to treat vaginal dysbiosis [50,150]. However, research on VMT is still in its infancy, even though a recent review [19] discussed an early study by Gardner and Dukes [151], where *Gardnerella vaginalis* was transferred by direct inoculation of material from the vaginas of infected women into the vaginas of healthy volunteers that developed diseased after transfer, as the first "successful" VMT. This clearly indicates that cautions have to be taken to avoid the transfer of any unwanted microorganism or agent when the aim is to treat a disease. In accordance, a universal donor screening approach has recently been implemented in a small pilot study [152]. The potential of VMT is also supported by epidemiological evidence provided by various studies showing that vaginal microbiota is transferred between women who have sex with women through sexual practice [19,153]. An exploratory study evaluating the use of VMT from healthy donors in a small number of patients suffering from intractable bacterial vaginosis has shown full long-term remission in most of the patients [50]. However, the efficacy of VMT for the treatment of bacterial vaginosis needs to be further validated in randomized, placebo-controlled clinical trials.

A related approach is the so-called 'vaginal seeding' where a cotton gauze or a cotton swab inoculated with vaginal fluids of the mother is used to transfer the vaginal microbiota to the mouth, nose, or skin of a newborn infant [154]. This approach is based on the observation that neonates born by caesarian section have different microbiome composition than those vaginally delivered [155,156] and also fewer maternally-delivered strains [157]. The altered microbiome in infants born by caesarian section has been

suggested to increase the risk to suffer later from obesity, asthma, allergies, and immune deficiencies [158]. Despite the potential benefits, the procedure of vaginal seeding has raised concern about its safety and infection risks to neonates need further exploration [159].

Manipulation of the microbiota may also be a promising strategy to manage urinary tract infections (UTIs). In fact, the human urinary tract has now been reported to contain a specific microbiota [160] and, therefore, an UTI may also be considered as a urinary tract dysbiosis [161]. Traditionally, UTIs are treated with antibiotics to achieve sterility. However, antibiotic treatment results not only in the elimination of pathogens but also of beneficial, protective microbial populations. Modulation of the urinary tract microbiota by probiotics may thus be an alternative strategy to treat UTI. In this regard, a moderate reduction in the incidence of UTI has been observed in patients receiving a vaginal *L. crispatus* probiotic [162]. Additional reports have confirmed the usefulness of vaginal suppositories containing *L crispatus* to reduce colonization by uropathogenic bacteria [163]. Given the interconnection between urinary tract and vaginal microbiota, also a VMT is discussed for the treatment of UTIs, but this strategy has not been explored yet. FMT has also been reported to reduce UTI frequency in CDI patients [164]. Even though the mechanism underlying this phenomenon is not yet clear, it is assumed that FMT reduces the abundance of uropathogens in the gut, which is a risk factor for UTIs [165].

8. Microbiome transplantation and cancer

Dysbiosis has been implicated in the pathophysiology of several types of cancer [166–168]. The influence of commensal bacteria in cancer progression seems to be mediated by their metabolic activities and their modulation of immune cells and inflammation. For example, several studies have provided evidence that butyrate, a short-chain fatty acid produced by bacterial fermentation of fiber in the colon, exhibits anti-cancer activity in colorectal cancer [169,170]. Patients with colorectal cancer have lower levels of butyrate producers in the gut microbiota than healthy individuals [170,171].

Immunotherapy, which involves targeted immune-based strategies that enhance the capacity of the immune system to destroy cancer cells, has emerged as a powerful tool for cancer treatment [172]. However, the efficacy and adverse side effects of immunotherapy among cancer patients are highly variable [173]. Although the precise reason for this variability is still unclear, several studies indicated a potential influence of the gut microbiota in the inter-individual variability in the outcome of cancer immunotherapy [174,175]. Further evidence for a role of the microbiota in cancer immunotherapy has been provided by the increased response of germ-free mice to immunotherapy after FMT from responding patients [176]. Antibiotics are routinely given to patients undergoing immunotherapy to reduce the risk of infection. Long-term antibiotic therapy can cause gut dysbiosis and several studies have reported an association of antibiotic treatment and poor immunotherapy outcomes [177–179]. Therefore, replenishment of commensal bacterial populations with beneficial bacteria may improve the response in cancer patients undergoing immunotherapy. In this regard, a clinical trial conducted with patients after bone marrow transplantation showed that transfer of autologous fecal microbiota collected before transplantation could in most of the cases reconstitute the microbiota composition and diversity that the patients originally had [180]. First-in-human clinical trials are currently ongoing to test the potential of FMT to improve the response of patients with PD-1-refractory melanoma to immunotherapy [49,181]. The results of these studies indicate that FMT changed the gut microbiome and reprogrammed the tumor microenvironment to overcome primary resistance to anti–PD-1 in a subset of patients with advanced melanoma [49,181]. Although these studies provide proof-of-concept evidence for the beneficial effect of FMT in cancer patients, this procedure will only be implemented in clinical practice after the precise molecular mechanisms underlying this effect are uncovered.

9. Summary and outlook

The benefits of microbiome transplantation for the treatment of many pathological disorders are now undeniable. However, the transfer of live microorganisms from healthy donors to patients is not without risk. In this regard, regulatory standards on screening for pathogens need to be implemented to diminish the risk of transferring microorganisms with pathogenic potential, in particular those carrying antibiotic resistances. Furthermore, standardization of methods, techniques and processes for microbiome collection, preparation and storage across the different centers will be critical for estimating the efficacy of microbiome transplantation in the different clinical studies. Efforts in this direction are currently under way [84].

The future of microbiota-based therapeutics will be the administration of rationally well-defined consortia of microorganisms that have been selected based on their beneficial effect rather than entire microbiomes. This will require a precise characterization of the microbial community members in health and during dysbiosis in disease conditions. Prospective studies where the microbiome is characterized in all participant individuals prior to the occurrence of disease will facilitate the establishment of a causative effect of dysbiosis on disease. Targeting the microbiome pathofunctions may be also an important area of research in the future. Therefore, future research should aim at getting a better understanding of the interactions between the microbiome and their host as well as the interactions between the different members of the consortia that underlie microbiome assembly and functionality in healthy and pathological settings. Based on this knowledge, therapeutic or preventive strategies can be developed to target the specific pathological functions of the microbiota in a more personalized fashion.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This work was financially supported by internal funding provided by the Helmholtz Centre for Infection Research.

References

[1] Berg G, Rybakova D, Fischer D, Cernava T, Verges MC, Charles T, et al. Microbiome definition re-visited: old concepts and new challenges. Microbiome. 2020;8(1):103. Epub 2020/07/02. doi: 10.1186/s40168-020-00875-0. PubMed PMID: 32605663; PubMed Central PMCID: PMCPMC7329523.

[2] Nishida A, Inoue R, Inatomi O, Bamba S, Naito Y, Andoh A. Gut microbiota in the pathogenesis of inflammatory bowel disease. Clin J Gastroenterol. 2018;11(1):1-10. Epub 2017/12/30. doi: 10.1007/s12328-017-0813-5. PubMed PMID: 29285689.

[3] Pascal M, Perez-Gordo M, Caballero T, Escribese MM, Lopez Longo MN, Luengo O, et al. Microbiome and allergic diseases. Front Immunol. 2018;9:1584. Epub 2018/08/02. doi: 10.3389/fimmu.2018.01584. PubMed PMID: 30065721; PubMed Central PMCID: PMCPMC6056614.

[4] Amabebe E, Robert FO, Agbalalah T, Orubu ESF. Microbial dysbiosis-induced obesity: role of gut microbiota in homoeostasis of energy metabolism. Br J

Nutr. 2020;123(10):1127-37. Epub 2020/02/06. doi: 10.1017/S0007114520000380. PubMed PMID: 32008579.
[5] Ahmadmehrabi S, Tang WHW. Gut microbiome and its role in cardiovascular diseases. Curr Opin Cardiol. 2017;32(6):761-6. Epub 2017/10/13. doi: 10.1097/HCO.0000000000000044PubMed PMID: 29023288; PubMed Central PMCID: PMCPMC5746314.
[6] Ooijevaar RE, Terveer EM, Verspaget HW, Kuijper EJ, Keller JJ. Clinical application and potential of fecal microbiota transplantation. Annu Rev Med. 2019;70:335-51. Epub 2018/11/08. doi: 10.1146/annurev-med-111717-12295PubMed PMID: 30403550.
[7] Zhang F, Luo W, Shi Y, Fan Z, Ji G. Should we standardize the 1,700-year-old fecal microbiota transplantation? Am J Gastroenterol. 2012;107(11):1755; author reply p -6. Epub 2012/11/20. doi: 10.1038/ajg.2012.251. PubMed PMID: 23160295.
[8] Zhang F, Cui B, He X, Nie Y, Wu K, Fan D, et al. Microbiota transplantation: concept, methodology and strategy for its modernization. Protein Cell. 2018;9(5):462-73. Epub 2018/04/25. doi: 10.1007/s13238-018-0541-PubMed PMID: 29691757; PubMed Central PMCID: PMCPMC5960466.
[9] van Nood E, Dijkgraaf MG, Keller JJ. Duodenal infusion of feces for recurrent *Clostridium difficile*. N Engl J Med. 2013;368(22):2145. Epub 2013/05/31. doi: 10.1056/NEJMc130391PubMed PMID: 23718168.
[10] Cammarota G, Masucci L, Ianiro G, Bibbo S, Dinoi G, Costamagna G, et al. Randomised clinical trial: faecal microbiota transplantation by colonoscopy vs. vancomycin for the treatment of recurrent *Clostridium difficile* infection. Aliment Pharmacol Ther. 2015;41(9):835-43. Epub 2015/03/03. doi: 10.1111/apt.13144. PubMed PMID: 25728808.
[11] Tariq R, Hayat M, Pardi D, Khanna S. Predictors of failure after fecal microbiota transplantation for recurrent *Clostridioides difficile* infection: a systematic review and meta-analysis. Eur J Clin Microbiol Infect Dis. 2021;40(7):1383-92. Epub 2021/01/27. doi: 10.1007/s10096-021-04163-z. PubMed PMID: 33496893.
[12] Goldenberg SD, Merrick B. The role of faecal microbiota transplantation: looking beyond *Clostridioides difficile* infection. Ther Adv Infect Dis. 2021;8:2049936120981526. Epub 2021/02/23. doi: 10.1177/2049936120981526. PubMed PMID: 33614028; PubMed Central PMCID: PMCPMC7841662.
[13] Zhou HY, Guo B, Lufumpa E, Li XM, Chen LH, Meng X, et al. Comparative of the effectiveness and safety of biological agents, tofacitinib, and fecal microbiota transplantation in ulcerative colitis: systematic review and network meta-analysis. Immunol Invest. 2021;50(4):323-37. Epub 2020/02/06. doi: 10.1080/08820139.2020.1714650. PubMed PMID: 32009472.
[14] Sokol H, Landman C, Seksik P, Berard L, Montil M, Nion-Larmurier I, et al. Fecal microbiota transplantation to maintain remission in Crohn's disease: a pilot randomized controlled study. Microbiome. 2020;8(1):12. Epub 2020/02/06. doi: 10.1186/s40168-020-0792-5. PubMed PMID: 32014035; PubMed Central PMCID: PMCPMC6998149.
[15] Stallmach A, Lange K, Buening J, Sina C, Vital M, Pieper DH. Fecal microbiota transfer in patients with chronic antibiotic-refractory pouchitis. Am J Gastroenterol. 2016;111(3):441-3. Epub 2016/03/29. doi: 10.1038/ajg.2015.436. PubMed PMID: 27018122.
[16] Hanssen NMJ, de Vos WM, Nieuwdorp M. Fecal microbiota transplantation in human metabolic diseases: From a murky past to a bright future? Cell Metab. 2021;33(6):1098-110. Epub 2021/06/03. doi: 10.1016/j.cmet.2021.05.005. PubMed PMID: 34077717.
[17] Vendrik KEW, Ooijevaar RE, de Jong PRC, Laman JD, van Oosten BW, van Hilten JJ, et al. Fecal microbiota transplantation in neurological disorders. Front Cell Infect Microbiol. 2020;10:98. Epub 2020/04/09. doi: 10.3389/fcimb.2020.00098. PubMed PMID: 32266160; PubMed Central PMCID: PMCPMC7105733.
[18] Myles IA, Earland NJ, Anderson ED, Moore IN, Kieh MD, Williams KW, et al. First-in-human topical microbiome transplantation with *Roseomonas mucosa* for atopic dermatitis. JCI Insight. 2018;3(9). Epub 2018/05/04. doi: 10.1172/jci.insight.120608. PubMed PMID: 29720571; PubMed Central PMCID: PMCPMC6012572.
[19] DeLong K, Zulfiqar F, Hoffmann DE, Tarzian AJ, Ensign LM. Vaginal microbiota transplantation: The Next Frontier. J Law Med Ethics. 2019;47(4):555-67. Epub 2020/01/21. doi: 10.1177/1073110519897731. PubMed PMID: 31957577.
[20] Turnbaugh PJ, Ley RE, Hamady M, Fraser-Liggett CM, Knight R, Gordon JI. The human microbiome project. Nature. 2007;449(7164):804-10. Epub 2007/10/19. doi: 10.1038/nature06244. PubMed PMID: 17943116; PubMed Central PMCID: PMCPMC3709439.
[21] Methé BA, Nelson KE, Pop M, Creasy HH, Giglio MG, Huttenhower C, et al. A framework for human microbiome research. Nature 2012;486(7402):215–21. https://doi.org/10.1038/nature11209.
[22] Costello EK, Stagaman K, Dethlefsen L, Bohannan BJ, Relman DA. The application of ecological theory toward an understanding of the human microbiome. Science. 2012;336(6086):1255-62. Epub 2012/06/08. doi: 10.1126/science.1224203. PubMed PMID: 22674335; PubMed Central PMCID: PMCPMC4208626.
[23] An R, Wilms E, Masclee AAM, Smidt H, Zoetendal EG, Jonkers D. Age-dependent changes in GI physiology and microbiota: time to reconsider? Gut. 2018;67(12):2213-22. Epub 2018/09/09. doi: 10.1136/gutjnl-2017-315542. PubMed PMID: 30194220.
[24] Pasolli E, Asnicar F, Manara S, Zolfo M, Karcher N, Armanini F, et al. Extensive unexplored human microbiome diversity revealed by over 150,000 genomes from metagenomes spanning age, geography, and lifestyle. Cell. 2019;176(3):649-62 e20. doi: 10.1016/j.cell.2019.01.001. PubMed PMID: 30661755; PubMed Central PMCID: PMCPMC6349461.
[25] Yatsunenko T, Rey FE, Manary MJ, Trehan I, Dominguez-Bello MG, Contreras M, et al. Human gut microbiome viewed across age and geography. Nature 2012;486(7402):222–7. https://doi.org/10.1038/nature11053. PubMed PMID: 22699611; PubMed Central PMCID: PMCPMC3376388.
[26] Vital M, Karch A, Pieper DH. Colonic butyrate-producing communities in humans: an overview using omics data. mSystems. 2017;2(6). Epub 2017/12/15. doi: 10.1128/mSystems.00130-17. PubMed PMID: 29238752; PubMed Central PMCID: PMCPMC5715108.
[27] Duvallet C, Gibbons SM, Gurry T, Irizarry RA, Alm EJ. Meta-analysis of gut microbiome studies identifies disease-specific and shared responses. Nat Commun. 2017;8(1):1784. Epub 2017/12/07. doi: 10.1038/s41467-017-01973-8. PubMed PMID: 29209090; PubMed Central PMCID: PMCPMC5716994.
[28] Ternes D, Karta J, Tsenkova M, Wilmes P, Haan S, Letellier E. Microbiome in colorectal cancer: how to get from meta-omics to mechanism? Trends Microbiol. 2020;28(5):401-23. Epub 2020/02/13. doi: 10.1016/j.tim.2020.01.001. PubMed PMID: 32298617.
[29] Qin J, Li Y, Cai Z, Li S, Zhu J, Zhang F, et al. A metagenome-wide association study of gut microbiota in type 2 diabetes. Nature. 2012;490(7418):55-60. Epub 2012/10/02. doi: 10.1038/nature11450. PubMed PMID: 23023125.
[30] Tiffany CR, Baumler AJ. Dysbiosis: from fiction to function. Am J Physiol Gastrointest Liver Physiol. 2019;317(5):G602-G8. Epub 2019/09/12. doi: 10.1152/ajpgi.00230.2019. PubMed PMID: 31509433; PubMed Central PMCID: PMCPMC6879887.
[31] Belizario JE, Napolitano M. Human microbiomes and their roles in dysbiosis, common diseases, and novel therapeutic approaches. Front Microbiol. 2015;6:1050. Epub 2015/10/27. doi: 10.3389/fmicb.2015.01050. PubMed PMID: 26500616; PubMed Central PMCID: PMCPMC4594012.
[32] Vayssier-Taussat M, Albina E, Citti C, Cosson JF, Jacques MA, Lebrun MH, et al. Shifting the paradigm from pathogens to pathobiome: new concepts in the light of meta-omics. Front Cell Infect Microbiol. 2014;4:29. Epub 2014/03/19. doi: 10.3389/fcimb.2014.00029. PubMed PMID: 24634890; PubMed Central PMCID: PMCPMC3942874.
[33] Wilkins LJ, Monga M, Miller AW. Defining dysbiosis for a cluster of chronic diseases. Sci Rep. 2019;9(1):12918. Epub 2019/09/11. doi: 10.1038/s41598-019-49452-y. PubMed PMID: 31501492; PubMed Central PMCID: PMCPMC6733864.
[34] Rath S, Rud T, Karch A, Pieper DH, Vital M. Pathogenic functions of host microbiota. Microbiome. 2018;6(1):174. Epub 2018/09/30. doi: 10.1186/s40168-018-0542-0. PubMed PMID: 30266099; PubMed Central PMCID: PMCPMC6162913.
[35] Tang WH, Wang Z, Levison BS, Koeth RA, Britt EB, Fu X, et al. Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. N Engl J Med. 2013;368(17):1575-84. Epub 2013/04/26. doi: 10.1056/NEJMoa1109400. PubMed PMID: 23614584; PubMed Central PMCID: PMCPMC3701945.
[36] Rath S, Heidrich B, Pieper DH, Vital M. Uncovering the trimethylamine-producing bacteria of the human gut microbiota. Microbiome. 2017;5(1):54. https://doi.org/10.1186/s40168-017-0271-9. PubMed PMID: 28506279; PubMed Central PMCID: PMCPMC5433236.
[37] Morais LH, Schreiber HLt, Mazmanian SK. The gut microbiota-brain axis in behaviour and brain disorders. Nat Rev Microbiol. 2021;19(4):241-55. Epub 2020/10/24. doi: 10.1038/s41579-020-00460-0. PubMed PMID: 33093662.
[38] Agus A, Clement K, Sokol H. Gut microbiota-derived metabolites as central regulators in metabolic disorders. Gut. 2021;70(6):1174-82. Epub 2020/12/05. doi: 10.1136/gutjnl-2020-323071. PubMed PMID: 33272977; PubMed Central PMCID: PMCPMC8108286.
[39] O'Mahony SM, Clarke G, Borre YE, Dinan TG, Cryan JF. Serotonin, tryptophan metabolism and the brain-gut-microbiome axis. Behav Brain Res. 2015;277:32-48. Epub 2014/08/01. doi: 10.1016/j.bbr.2014.07.027. PubMed PMID: 25078296.
[40] Jangi S, Gandhi R, Cox LM, Li N, von Glehn F, Yan R, et al. Alterations of the human gut microbiome in multiple sclerosis. Nat Commun. 2016;7:12015. https://doi.org/10.1038/ncomms12015. PubMed PMID: 27352007; PubMed Central PMCID: PMCPMC4931233.
[41] Strati F, Cavalieri D, Albanese D, De Felice C, Donati C, Hayek J, et al. New evidences on the altered gut microbiota in autism spectrum disorders. Microbiome. 2017;5(1):24. https://doi.org/10.1186/s40168-017-0242-1. PubMed PMID: 28222761; PubMed Central PMCID: PMCPMC5320696.
[42] Valles-Colomer M, Falony G, Darzi Y, Tigchelaar EF, Wang J, Tito RY, et al. The neuroactive potential of the human gut microbiota in quality of life and depression. Nat Microbiol. 2019;4(4):623-32. Epub 2019/02/06. doi: 10.1038/s41564-018-0337-x. PubMed PMID: 30718848.
[43] Vascellari S, Palmas V, Melis M, Pisanu S, Cusano R, Uva P, et al. Gut microbiota and metabolome alterations associated with Parkinson's disease. mSystems. 2020;5(5). Epub 2020/09/17. doi: 10.1128/mSystems.00561-20. PubMed PMID: 32934117; PubMed Central PMCID: PMCPMC7498685.
[44] Baker JM, Al-Nakkash L, Herbst-Kralovetz MM. Estrogen-gut microbiome axis: Physiological and clinical implications. Maturitas. 2017;103:45-53. Epub 2017/08/06. doi: 10.1016/j.maturitas.2017.06.025. PubMed PMID: 28778332.
[45] Zheng D, Liwinski T, Elinav E. Interaction between microbiota and immunity in health and disease. Cell Res. 2020;30(6):492-506. Epub 2020/05/21. doi:

10.1038/s41422-020-0332-7. PubMed PMID: 32433595; PubMed Central PMCID: PMCPMC7264227.
[46] Cammarota G, Ianiro G, Gasbarrini A. Fecal microbiota transplantation for the treatment of *Clostridium difficile* infection: a systematic review. J Clin Gastroenterol. 2014;48(8):693-702. Epub 2014/01/21. doi: 10.1097/MCG.0000000000000PubMed PMID: 24440934.
[47] Rossen NG, Fuentes S, van der Spek MJ, Tijssen JG, Hartman JH, Duflou A, et al. Findings from a randomized controlled trial of fecal transplantation for patients with ulcerative colitis. Gastroenterology 2015;149(1):110–8 e4. https://doi.org/10.1053/j.gastro.2015.03.045. PubMed PMID: 25836986.
[48] Suskind DL, Brittnacher MJ, Wahbeh G, Shaffer ML, Hayden HS, Qin X, et al. Fecal microbial transplant effect on clinical outcomes and fecal microbiome in active Crohn's disease. Inflamm Bowel Dis. 2015;21(3):556-63. Epub 2015/02/04. doi: 10.1097/MIB.0000000000000307. PubMed PMID: 25647155; PubMed Central PMCID: PMCPMC4329080.
[49] Baruch EN, Youngster I, Ben-Betzalel G, Ortenberg R, Lahat A, Katz L, et al. Fecal microbiota transplant promotes response in immunotherapy-refractory melanoma patients. Science. 2021;371(6529):602-9. Epub 2020/12/12. doi: 10.1126/science.abb5920. PubMed PMID: 33303685.
[50] Lev-Sagie A, Goldman-Wohl D, Cohen Y, Dori-Bachash M, Leshem A, Mor U, et al. Vaginal microbiome transplantation in women with intractable bacterial vaginosis. Nat Med. 2019;25(10):1500-4. Epub 2019/10/09. doi: 10.1038/s41591-019-0600-6. PubMed PMID: 31591599.
[51] Falony G, Joossens M, Vieira-Silva S, Wang J, Darzi Y, Faust K, et al. Population-level analysis of gut microbiome variation. Science. 2016;352(6285):560-4. Epub 2016/04/30. doi: 10.1126/science.aad3503. PubMed PMID: 27126039.
[52] Mancabelli L, Milani C, Lugli GA, Turroni F, Ferrario C, van Sinderen D, et al. Meta-analysis of the human gut microbiome from urbanized and pre-agricultural populations. Environ Microbiol. 2017;19(4):1379-90. Epub 2017/02/16. doi: 10.1111/1462-2920.13692. PubMed PMID: 28198087.
[53] Ridaura VK, Faith JJ, Rey FE, Cheng J, Duncan AE, Kau AL, et al. Gut microbiota from twins discordant for obesity modulate metabolism in mice. Science. 2013;341(6150):1241214. Epub 2013/09/07. doi: 10.1126/science.1241214. PubMed PMID: 24009397; PubMed Central PMCID: PMCPMC3829625.
[54] Sharon G, Cruz NJ, Kang DW, Gandal MJ, Wang B, Kim YM, et al. Human gut microbiota from autsism spectrum disorder promote behavioral symptoms in mice. Cell. 2019;177(6):1600-18 e17. Epub 2019/06/01. doi: 10.1016/j.cell.2019.05.004. PubMed PMID: 31150625; PubMed Central PMCID: PMCPMC6993574.
[55] De Palma G, Lynch MD, Lu J, Dang VT, Deng Y, Jury J, et al. Transplantation of fecal microbiota from patients with irritable bowel syndrome alters gut function and behavior in recipient mice. Sci Transl Med. 2017;9(379). Epub 2017/03/03. doi: 10.1126/scitranslmed.aaf6397. PubMed PMID: 28251905.
[56] Wos-Oxley M, Bleich A, Oxley AP, Kahl S, Janus LM, Smoczek A, et al. Comparative evaluation of establishing a human gut microbial community within rodent models. Gut Microbes. 2012;3(3):234-49. Epub 2012/05/11. doi: 10.4161/gmic.19934. PubMed PMID: 22572831; PubMed Central PMCID: PMCPMC3427216.
[57] Hintze KJ, Cox JE, Rompato G, Benninghoff AD, Ward RE, Broadbent J, et al. Broad scope method for creating humanized animal models for animal health and disease research through antibiotic treatment and human fecal transfer. Gut Microbes. 2014;5(2):183-91. Epub 2014/03/19. doi: 10.4161/gmic.28403. PubMed PMID: 24637796; PubMed Central PMCID: PMCPMC4063843.
[58] Arrieta MC, Walter J, Finlay BB. Human microbiota-associated mice: a model with challenges. Cell Host Microbe. 2016;19(5):575-8. Epub 2016/05/14. doi: 10.1016/j.chom.2016.04.014. PubMed PMID: 27173924.
[59] Li SS, Zhu A, Benes V, Costea PI, Hercog R, Hildebrand F, et al. Durable coexistence of donor and recipient strains after fecal microbiota transplantation. Science. 2016;352(6285):586-9. Epub 2016/04/30. doi: 10.1126/science.aad8852. PubMed PMID: 27126044.
[60] Smillie CS, Sauk J, Gevers D, Friedman J, Sung J, Youngster I, et al. Strain tracking reveals the determinants of bacterial engraftment in the human gut following fecal microbiota transplantation. Cell Host Microbe. 2018;23(2):229-40 e5. Epub 2018/02/16. doi: 10.1016/j.chom.2018.01.003. PubMed PMID: 29447696; PubMed Central PMCID: PMCPMC8318347.
[61] Johnson JS, Spakowicz DJ, Hong BY, Petersen LM, Demkowicz P, Chen L, et al. Evaluation of 16S rRNA gene sequencing for species and strain-level microbiome analysis. Nat Commun. 2019;10(1):5029. Epub 2019/11/07. doi: 10.1038/s41467-019-13036-1. PubMed PMID: 31695033; PubMed Central PMCID: PMCPMC6834636.
[62] Schulz C, Schutte K, Koch N, Vilchez-Vargas R, Wos-Oxley ML, Oxley APA, et al. The active bacterial assemblages of the upper GI tract in individuals with and without Helicobacter infection. Gut. 2018;67(2):216-25. Epub 2016/12/07. doi: 10.1136/gutjnl-2016-312904. PubMed PMID: 27920199.
[63] Langille MG, Zaneveld J, Caporaso JG, McDonald D, Knights D, Reyes JA, et al. Predictive functional profiling of microbial communities using 16S rRNA marker gene sequences. Nat Biotechnol. 2013;31(9):814-21. Epub 2013/08/27. doi: 10.1038/nbt.2676. PubMed PMID: 23975157; PubMed Central PMCID: PMCPMC3819121.
[64] Asshauer KP, Wemheuer B, Daniel R, Meinicke P. Tax4Fun: predicting functional profiles from metagenomic 16S rRNA data. Bioinformatics. 2015;31(17):2882-4. Epub 2015/05/10. doi: 10.1093/bioinformatics/btv287. PubMed PMID: 25957349; PubMed Central PMCID: PMCPMC4547618.
[65] Quince C, Walker AW, Simpson JT, Loman NJ, Segata N. Shotgun metagenomics, from sampling to analysis. Nat Biotechnol. 2017;35(9):833-44. Epub 2017/09/13. doi: 10.1038/nbt.3935. PubMed PMID: 28898207.
[66] Bashiardes S, Zilberman-Schapira G, Elinav E. Use of metatranscriptomics in microbiome research. Bioinform Biol Insights. 2016;10:19-25. Epub 2016/04/30. doi: 10.4137/BBI.S34610. PubMed PMID: 27127406; PubMed Central PMCID: PMCPMC4839964.
[67] Marotz C, Cavagnero KJ, Song SJ, McDonald D, Wandro S, Humphrey G, et al. Evaluation of the effect of storage methods on fecal, saliva, and skin microbiome composition. mSystems. 2021;6(2). Epub 2021/04/29. doi: 10.1128/mSystems.01329-20. PubMed PMID: 33906915; PubMed Central PMCID: PMCPMC8092129.
[68] Kazantseva J, Malv E, Kaleda A, Kallastu A, Meikas A. Optimisation of sample storage and DNA extraction for human gut microbiota studies. BMC Microbiol. 2021;21(1):158. Epub 2021/05/31. doi: 10.1186/s12866-021-02233-y. PubMed PMID: 34051731; PubMed Central PMCID: PMCPMC8164492.
[69] Young RR, Jenkins K, Araujo-Perez F, Seed PC, Kelly MS. Long-term stability of microbiome diversity and composition in fecal samples stored in eNAT medium. Microbiologyopen. 2020;9(7):e1046. Epub 2020/05/12. doi: 10.1002/mbo3.1046. PubMed PMID: 32390344; PubMed Central PMCID: PMCPMC7349174.
[70] Karstens L, Asquith M, Davin S, Fair D, Gregory WT, Wolfe AJ, et al. Controlling for contaminants in low-biomass 16S rRNA gene sequencing experiments. mSystems. 2019;4(4). doi: 10.1128/mSystems.00290-19. PubMed PMID: 31164452; PubMed Central PMCID: PMCPMC6550369.
[71] Kim D, Hofstaedter CE, Zhao C, Mattei L, Tanes C, Clarke E, et al. Optimizing methods and dodging pitfalls in microbiome research. Microbiome. 2017;5(1):52. Epub 2017/05/10. doi: 10.1186/s40168-017-0267-5. PubMed PMID: 28476139; PubMed Central PMCID: PMCPMC5420141.
[72] Wos-Oxley ML, Plumeier I, von Eiff C, Taudien S, Platzer M, Vilchez-Vargas R, et al. A poke into the diversity and associations within human anterior nare microbial communities. ISME J. 2010;4(7):839-51. Epub 2010/02/26. doi: 10.1038/ismej.2010.15. PubMed PMID: 20182526.
[73] Roberts RJ, Carneiro MO, Schatz MC. The advantages of SMRT sequencing. Genome Biol. 2013;14(7):405. Epub 2013/07/05. doi: 10.1186/gb-2013-14-6-405. PubMed PMID: 23822731; PubMed Central PMCID: PMCPMC3953343.
[74] Callahan BJ, McMurdie PJ, Rosen MJ, Han AW, Johnson AJ, Holmes SP. DADA2: High-resolution sample inference from Illumina amplicon data. Nat Methods. 2016;13(7):581–3. https://doi.org/10.1038/nmeth.3869. PubMed PMID: 27214047; PubMed Central PMCID: PMCPMC4927377.
[75] Cole JR, Wang Q, Fish JA, Chai B, McGarrell DM, Sun Y, et al. Ribosomal Database Project: data and tools for high throughput rRNA analysis. Nucleic Acids Res. 2014;42(Database issue):D633-42. Epub 2013/11/30. doi: 10.1093/nar/gkt1244. PubMed PMID: 24288368; PubMed Central PMCID: PMCPMC3965039.
[76] Glockner FO, Yilmaz P, Quast C, Gerken J, Beccati A, Ciuprina A, et al. 25 years of serving the community with ribosomal RNA gene reference databases and tools. J Biotechnol. 2017;261:169-Epub 2017/06/27. doi: 10.1016/j.jbiotec.2017.06.1198. PubMed PMID: 28648396.
[77] Kleine Bardenhorst S, Berger T, Klawonn F, Vital M, Karch A, Rubsamen N. Data analysis strategies for microbiome studies in human populations-a systematic review of current practice. mSystems. 2021;6(1).;Epub 2021/02/25. https://doi.org/10.1128/mSystems.01154-20. PubMed PMID: 33622856.
[78] Sczyrba A, Hofmann P, Belmann P, Koslicki D, Janssen S, Droge J, et al. Critical assessment of metagenome interpretation-a benchmark of metagenomics software. Nat Methods. 2017;14(11):1063-71. Epub 2017/10/03. doi: 10.1038/nmeth.4458. PubMed PMID: 28967888; PubMed Central PMCID: PMCPMC5903868.
[79] Schnoes AM, Brown SD, Dodevski I, Babbitt PC. Annotation error in public databases: misannotation of molecular function in enzyme superfamilies. PLoS Comput Biol. 2009;5(12):e1000605. Epub 2009/12/17. doi: 10.1371/journal.pcbi.1000605. PubMed PMID: 20011109; PubMed Central PMCID: PMCPMC2781113.
[80] Wei X, Zhang C, Freddolino PL, Zhang Y. Detecting Gene Ontology misannotations using taxon-specific rate ratio comparisons. Bioinformatics. 2020;36(16):4383-8. Epub 2020/05/30. doi: 10.1093/bioinformatics/btaa548. PubMed PMID: 32470107; PubMed Central PMCID: PMCPMC7751014.
[81] Cold F, Baunwall SMD, Dahlerup JF, Petersen AM, Hvas CL, Hansen LH. Systematic review with meta-analysis: encapsulated faecal microbiota transplantation - evidence for clinical efficacy. Therap Adv Gastroenterol. 2021;14:17562848211041004. Epub 2021/09/07. doi: 10.1177/17562848211041004. PubMed PMID: 34484424; PubMed Central PMCID: PMCPMC8414624.
[82] Hamilton MJ, Weingarden AR, Sadowsky MJ, Khoruts A. Standardized frozen preparation for transplantation of fecal microbiota for recurrent *Clostridium difficile* infection. Am J Gastroenterol. 2012;107(5):761–7. https://doi.org/10.1038/ajg.2011.482. PubMed PMID: 22290405.
[83] Staley C, Kaiser T, Vaughn BP, Graiziger CT, Hamilton MJ, Rehman TU, et al. Predicting recurrence of *Clostridium difficile* infection following encapsulated fecal microbiota transplantation. Microbiome. 2018;6(1):166. https://doi.org/10.1186/s40168-018-0549-6. PubMed PMID: 30227892.
[84] Cammarota G, Ianiro G, Tilg H, Rajilic-Stojanovic M, Kump P, Satokari R, et al. European consensus conference on faecal microbiota transplantation in clinical practice. Gut. 2017;66(4):569-80. Epub 2017/01/15. doi: 10.1136/

gutjnl-2016-313017. PubMed PMID: 28087657; PubMed Central PMCID: PMCPMC5529972.
[85] Ianiro G, Gasbarrini A, Cammarota G. Evaluating donor microbiome before fecal microbiota transplantation. Gastroenterology. 2021. Epub 2021/07/13. doi: 10.1053/j.gastro.2021.07.003. PubMed PMID: 34252410.
[86] DeFilipp Z, Bloom PP, Torres Soto M, Mansour MK, Sater MRA, Huntley MH, et al. Drug-resistant *E. coli* bacteremia transmitted by fecal microbiota transplant. N Engl J Med. 2019;381(21):2043-50. Epub 2019/10/31. doi: 10.1056/NEJMoa1910437. PubMed PMID: 31665575.
[87] Keller JJ, Ooijevaar RE, Hvas CL, Terveer EM, Lieberknecht SC, Hogenauer C, et al. A standardised model for stool banking for faecal microbiota transplantation: a consensus report from a multidisciplinary UEG working group. United European Gastroenterol J. 2021;9(2):229-47. Epub 2020/11/06. doi: 10.1177/2050640620967898. PubMed PMID: 33151137; PubMed Central PMCID: PMCPMC8259288.
[88] Cammarota G, Ianiro G, Kelly CR, Mullish BH, Allegretti JR, Kassam Z, et al. International consensus conference on stool banking for faecal microbiota transplantation in clinical practice. Gut. 2019;68(12):2111-21. Epub 2019/09/30. doi: 10.1136/gutjnl-2019-319548. PubMed PMID: 31563878; PubMed Central PMCID: PMCPMC6872442.
[89] Woodworth MH, Carpentieri C, Sitchenko KL, Kraft CS. Challenges in fecal donor selection and screening for fecal microbiota transplantation: A review. Gut Microbes. 2017;8(3):225-37. Epub 2017/01/28. doi: 10.1080/19490976.2017.1286006. PubMed PMID: 28129018; PubMed Central PMCID: PMCPMC5479407.
[90] Ianiro G, Mullish BH, Kelly CR, Sokol H, Kassam Z, Ng SC, et al. Screening of faecal microbiota transplant donors during the COVID-19 outbreak: suggestions for urgent updates from an international expert panel. Lancet Gastroenterol Hepatol. 2020;5(5):430-2. Epub 2020/03/21. doi: 10.1016/S2468-1253(20)30082-0. PubMed PMID: 32192627; PubMed Central PMCID: PMCPMC7104244.
[91] Pigneur B, Sokol H. Fecal microbiota transplantation in inflammatory bowel disease: the quest for the holy grail. Mucosal Immunol. 2016;9(6):1360-5. Epub 2016/07/28. doi: 10.1038/mi.2016.67. PubMed PMID: 27461176.
[92] Danne C, Rolhion N, Sokol H. Recipient factors in faecal microbiota transplantation: one stool does not fit all. Nat Rev Gastroenterol Hepatol. 2021;18(7):503-13. Epub 2021/04/29. doi: 10.1038/s41575-021-00441-5. PubMed PMID: 33907321.
[93] Nemoto H, Kataoka K, Ishikawa H, Ikata K, Arimochi H, Iwasaki T, et al. Reduced diversity and imbalance of fecal microbiota in patients with ulcerative colitis. Dig Dis Sci. 2012;57(11):2955–64. https://doi.org/10.1007/s10620-012-2236-y. PubMed PMID: 22623042.
[94] Vermeire S, Joossens M, Verbeke K, Wang J, Machiels K, Sabino J, et al. Donor species richness determines faecal microbiota transplantation success in inflammatory bowel disease. J Crohns Colitis. 2016;10(4):387–94. https://doi.org/10.1093/ecco-jcc/jjv203. PubMed PMID: 26519463; PubMed Central PMCID: PMCPMC4946755.
[95] Kump P, Wurm P, Grochenig HP, Wenzl H, Petritsch W, Halwachs B, et al. The taxonomic composition of the donor intestinal microbiota is a major factor influencing the efficacy of faecal microbiota transplantation in therapy refractory ulcerative colitis. Aliment Pharmacol Ther. 2018;47(1):67-77. Epub 2017/10/21. doi: 10.1111/apt.14387. PubMed PMID: 29052237; PubMed Central PMCID: PMCPMC5765501.
[96] Fujimoto T, Imaeda H, Takahashi K, Kasumi E, Bamba S, Fujiyama Y, et al. Decreased abundance of *Faecalibacterium prausnitzii* in the gut microbiota of Crohn's disease. J Gastroenterol Hepatol. 2013;28(4):613-9. Epub 2012/12/12. doi: 10.1111/jgh.12073. PubMed PMID: 23216550.
[97] Paramsothy S, Kamm MA, Kaakoush NO, Walsh AJ, van den Bogaerde J, Samuel D, et al. Multidonor intensive faecal microbiota transplantation for active ulcerative colitis: a randomised placebo-controlled trial. Lancet. 2017;389(10075):1218-28. Epub 2017/02/19. doi: 10.1016/S0140-6736(17)30182-4. PubMed PMID: 28214091.
[98] Wilson BC, Vatanen T, Cutfield WS, O'Sullivan JM. The super-donor phenomenon in fecal microbiota transplantation. Front Cell Infect Microbiol. 2019;9:2. Epub 2019/02/06. doi: 10.3389/fcimb.2019.00002. PubMed PMID: 30719428; PubMed Central PMCID: PMCPMC6348388.
[99] Weingarden A, Gonzalez A, Vazquez-Baeza Y, Weiss S, Humphry G, Berg-Lyons D, et al. Dynamic changes in short- and long-term bacterial composition following fecal microbiota transplantation for recurrent *Clostridium difficile* infection. Microbiome. 2015;3:10. Epub 2015/04/01. doi: 10.1186/s40168-015-0070-0. PubMed PMID: 25825673; PubMed Central PMCID: PMCPMC4378022.
[100] Moss EL, Falconer SB, Tkachenko E, Wang M, Systrom H, Mahabamunuge J, et al. Long-term taxonomic and functional divergence from donor bacterial strains following fecal microbiota transplantation in immunocompromised patients. PLoS One. 2017;12(8):e0182585. Epub 2017/08/23. doi: 10.1371/journal.pone.0182585. PubMed PMID: 28827811; PubMed Central PMCID: PMCPMC5565110.
[101] Sood A, Mahajan R, Singh A, Midha V, Mehta V, Narang V, et al. Role of faecal microbiota transplantation for maintenance of remission in patients with ulcerative colitis: a pilot study. J Crohns Colitis. 2019;13(10):1311-7. Epub 2019/03/16. doi: 10.1093/ecco-jcc/jjz060. PubMed PMID: 30873549.
[102] Goodrich JK, Waters JL, Poole AC, Sutter JL, Koren O, Blekhman R, et al. Human genetics shape the gut microbiome. Cell. 2014;159(4):789-99. Epub 2014/11/25. doi: 10.1016/j.cell.2014.09.053. PubMed PMID: 25417156; PubMed Central PMCID: PMCPMC4255478.
[103] Turpin W, Espin-Garcia O, Xu W, Silverberg MS, Kevans D, Smith MI, et al. Association of host genome with intestinal microbial composition in a large healthy cohort. Nat Genet. 2016;48(11):1413-7. Epub 2016/10/28. doi: 10.1038/ng.3693. PubMed PMID: 27694960.
[104] Ponce-Alonso M, Aguilera L, Rodriguez-de-Santiago E, Foruny JR, Roy G, DelCampo R, et al. P782 A new compatibility test for donor selection for faecal microbiota transplantation in ulcerative colitis. J Crohns Colitis 2017;11(1):S480–1. https://doi.org/10.1093/ecco-jcc/jjx002.903.
[105] Ponce-Alonso M, Garcia-Hoz C, Halperin A, Nuno J, Nicolas P, Martinez-Perez A, et al. An immunologic compatibility testing was not useful for donor selection in fecal microbiota transplantation for ulcerative colitis. Front Immunol. 2021;12:683387. Epub 2021/06/22. doi: 10.3389/fimmu.2021.683387. PubMed PMID: 34149723; PubMed Central PMCID: PMCPMC8212046.
[106] Huseyin CE, O'Toole PW, Cotter PD, Scanlan PD. Forgotten fungi-the gut mycobiome in human health and disease. FEMS Microbiol Rev. 2017;41(4):479-511. Epub 2017/04/22. doi: 10.1093/femsre/fuw047. PubMed PMID: 28430946.
[107] Sokol H, Leducq V, Aschard H, Pham HP, Jegou S, Landman C, et al. Fungal microbiota dysbiosis in IBD. Gut. 2017;66(6):1039-48. Epub 2016/02/05. doi: 10.1136/gutjnl-2015-310746. PubMed PMID: 26843508; PubMed Central PMCID: PMCPMC5532459.
[108] Coker OO, Nakatsu G, Dai RZ, Wu WKK, Wong SH, Ng SC, et al. Enteric fungal microbiota dysbiosis and ecological alterations in colorectal cancer. Gut. 2019;68(4):654-62. Epub 2018/11/26. doi: 10.1136/gutjnl-2018-317178. PubMed PMID: 30472682; PubMed Central PMCID: PMCPMC6580778.
[109] Leonardi I, Paramsothy S, Doron I, Semon A, Kaakoush NO, Clemente JC, et al. Fungal trans-kingdom dynamics linked to responsiveness to fecal microbiota transplantation (FMT) therapy in ulcerative colitis. Cell Host Microbe. 2020;27(5):823-9 e3. Epub 2020/04/17. doi: 10.1016/j.chom.2020.03.006. PubMed PMID: 32298656; PubMed Central PMCID: PMCPMC8647676.
[110] Ott SJ, Waetzig GH, Rehman A, Moltzau-Anderson J, Bharti R, Grasis JA, et al. Efficacy of sterile fecal filtrate transfer for treating patients with *Clostridium difficile* infection. Gastroenterology. 2017;152(4):799-811 e7. Epub 2016/11/22. doi: 10.1053/j.gastro.2016.11.010. PubMed PMID: 27866880.
[111] Rasmussen TS, Koefoed AK, Jakobsen RR, Deng L, Castro-Mejia JL, Brunse A, et al. Bacteriophage-mediated manipulation of the gut microbiome - promises and presents limitations. FEMS Microbiol Rev. 2020;44(4):507-21. Epub 2020/06/05. doi: 10.1093/femsre/fuaa020. PubMed PMID: 32495834.
[112] Zuo T, Wong SH, Lam K, Lui R, Cheung K, Tang W, et al. Bacteriophage transfer during faecal microbiota transplantation in *Clostridium difficile* infection is associated with treatment outcome. Gut. 2018;67(4):634-43. Epub 2017/05/26. doi: 10.1136/gutjnl-2017-313952. PubMed PMID: 28539351; PubMed Central PMCID: PMCPMC5868238.
[113] Fujimoto K, Kimura Y, Allegretti JR, Yamamoto M, Zhang YZ, Katayama K, et al. Functional restoration of bacteriomes and viromes by fecal microbiota transplantation. Gastroenterology. 2021;160(6):2089-102 e12. Epub 2021/02/13. doi: 10.1053/j.gastro.2021.02.013. PubMed PMID: 33577875; PubMed Central PMCID: PMCPMC8684800.
[114] Park H, Laffin MR, Jovel J, Millan B, Hyun JE, Hotte N, et al. The success of fecal microbial transplantation in *Clostridium difficile* infection correlates with bacteriophage relative abundance in the donor: a retrospective cohort study. Gut Microbes. 2019;10(6):676-87. Epub 2019/03/15. doi: 10.1080/19490976.2019.1586037. PubMed PMID: 30866714; PubMed Central PMCID: PMCPMC6867182.
[115] Clooney AG, Sutton TDS, Shkoporov AN, Holohan RK, Daly KM, O'Regan O, et al. Whole-virome analysis sheds light on viral dark matter in inflammatory bowel disease. Cell Host Microbe. 2019;26(6):764-78 e5. Epub 2019/11/24. doi: 10.1016/j.chom.2019.10.009. PubMed PMID: 31757768.
[116] Gogokhia L, Buhrke K, Bell R, Hoffman B, Brown DG, Hanke-Gogokhia C, et al. Expansion of bacteriophages Is linked to aggravated intestinal inflammation and Colitis. Cell Host Microbe. 2019;25(2):285-99 e8. Epub 2019/02/15. doi: 10.1016/j.chom.2019.01.008. PubMed PMID: 30763538; PubMed Central PMCID: PMCPMC6885004.
[117] Byrd AL, Belkaid Y, Segre JA. The human skin microbiome. Nat Rev Microbiol. 2018;16(3):143–55. https://doi.org/10.1038/nrmicro.2017.157. PubMed PMID: 29332945.
[118] Nakatsuji T, Chen TH, Narala S, Chun KA, Two AM, Yun T, et al. Antimicrobials from human skin commensal bacteria protect against *Staphylococcus aureus* and are deficient in atopic dermatitis. Sci Transl Med. 2017;9(378). Epub 2017/02/24. doi: 10.1126/scitranslmed.aah4680. PubMed PMID: 28228596; PubMed Central PMCID: PMCPMC5600545.
[119] Bjerre RD, Bandier J, Skov L, Engstrand L, Johansen JD. The role of the skin microbiome in atopic dermatitis: a systematic review. Br J Dermatol. 2017;177(5):1272-8. Epub 2017/02/17. doi: 10.1111/bjd.15390. PubMed PMID: 28207943.
[120] Lee YB, Byun EJ, Kim HS. Potential role of the microbiome in acne: a comprehensive review. J Clin Med. 2019;8(7). Epub 2019/07/10. doi: 10.3390/jcm8070987. PubMed PMID: 31284694; PubMed Central PMCID: PMCPMC6678709.
[121] Callewaert C, Knodlseder N, Karoglan A, Guell M, Paetzold B. Skin microbiome transplantation and manipulation: Current state of the art. Comput Struct Biotechnol J. 2021;19:624-31. Epub 2021/01/30. doi: 10.1016/j.csbj.2021.01.001. PubMed PMID: 33510866; PubMed Central PMCID: PMCPMC7806958.

[122] Hendricks AJ, Mills BW, Shi VY. Skin bacterial transplant in atopic dermatitis: Knowns, unknowns and emerging trends. J Dermatol Sci. 2019;95(2):56-61. Epub 2019/08/10. doi: 10.1016/j.jdermsci.2019.07.001. PubMed PMID: 31395434.
[123] Tham EH, Koh E, Common JEA, Hwang IY. Biotherapeutic approaches in atopic dermatitis. Biotechnol J. 2020;15(10):e1900322. Epub 2020/03/17. doi: 10.1002/biot.201900322. PubMed PMID: 32176834.
[124] Nodake Y, Matsumoto S, Miura R, Honda H, Ishibashi G, Matsumoto S, et al. Pilot study on novel skin care method by augmentation with *Staphylococcus epidermidis*, an autologous skin microbe–A blinded randomized clinical trial. J Dermatol Sci. 2015;79(2):119-26. Epub 2015/05/28. doi: 10.1016/j.jdermsci.2015.05.001. PubMed PMID: 26012780.
[125] Chin D, Goncheva MI, Flannagan RS, Deecker SR, Guariglia-Oropeza V, Ensminger AW, et al. Coagulase-negative staphylococci release a purine analog that inhibits *Staphylococcus aureus* virulence. Nat Commun. 2021;12(1):1887. Epub 2021/03/27. doi: 10.1038/s41467-021-22175-3. PubMed PMID: 33767207; PubMed Central PMCID: PMCPMC7994395.
[126] Nakatsuji T, Hata TR, Tong Y, Cheng JY, Shafiq F, Butcher AM, et al. Development of a human skin commensal microbe for bacteriotherapy of atopic dermatitis and use in a phase 1 randomized clinical trial. Nat Med. 2021;27(4):700-9. Epub 2021/02/24. doi: 10.1038/s41591-021-01256-2. PubMed PMID: 33619370; PubMed Central PMCID: PMCPMC8052297.
[127] Romano-Bertrand S, Bourdier A, Aujoulat F, Michon AL, Masnou A, Parer S, et al. Skin microbiota is the main reservoir of *Roseomonas mucosa*, an emerging opportunistic pathogen so far assumed to be environmental. Clin Microbiol Infect. 2016;22(8):737 e1-7. Epub 2016/06/09. doi: 10.1016/j.cmi.2016.05.024. PubMed PMID: 27269884.
[128] Myles IA, Williams KW, Reckhow JD, Jammeh ML, Pincus NB, Sastalla I, et al. Transplantation of human skin microbiota in models of atopic dermatitis. JCI Insight. 2016;1(10). Epub 2016/08/02. doi: 10.1172/jci.insight.86955. PubMed PMID: 27478874; PubMed Central PMCID: PMCPMC4963067.
[129] Karoglan A, Paetzold B, Pereira de Lima J, Bruggemann H, Tuting T, Schanze D, et al. Safety and efficacy of topically applied selected *Cutibacterium acnes* strains over five weeks in patients with acne vulgaris: an open-label, pilot study. Acta Derm Venereol. 2019;99(13):1253-7. Epub 2019/10/02. doi: 10.2340/00015555-3323. PubMed PMID: 31573666.
[130] Paetzold B, Willis JR, Pereira de Lima J, Knodlseder N, Bruggemann H, Quist SR, et al. Skin microbiome modulation induced by probiotic solutions. Microbiome. 2019;7(1):95. Epub 2019/06/27. doi: 10.1186/s40168-019-0709-3. PubMed PMID: 31234928; PubMed Central PMCID: PMCPMC6591853.
[131] Callewaert C, Lambert J, Van de Wiele T. Towards a bacterial treatment for armpit malodour. Exp Dermatol. 2017;26(5):388-91. Epub 2016/11/29. doi: 10.1111/exd.13259. PubMed PMID: 27892611.
[132] Troccaz M, Gaia N, Beccucci S, Schrenzel J, Cayeux I, Starkenmann C, et al. Mapping axillary microbiota responsible for body odours using a culture-independent approach. Microbiome. 2015;3(1):3. Epub 2015/02/06. doi: 10.1186/s40168-014-0064-3. PubMed PMID: 25653852; PubMed Central PMCID: PMC4316401.
[133] Ravel J, Gajer P, Abdo Z, Schneider GM, Koenig SS, McCulle SL, et al. Vaginal microbiome of reproductive-age women. Proc Natl Acad Sci U S A. 2011;108 Suppl 1:4680-7. Epub 2010/06/11. doi: 10.1073/pnas.1002611107. PubMed PMID: 20534435; PubMed Central PMCID: PMCPMC3063603.
[134] Hickey RJ, Zhou X, Pierson JD, Ravel J, Forney LJ. Understanding vaginal microbiome complexity from an ecological perspective. Transl Res. 2012;160(4):267-82. Epub 2012/06/12. doi: 10.1016/j.trsl.2012.02.008. PubMed PMID: 22683415; PubMed Central PMCID: PMCPMC3444549.
[135] Borges S, Silva J, Teixeira P. The role of lactobacilli and probiotics in maintaining vaginal health. Arch Gynecol Obstet. 2014;289(3):479-89. Epub 2013/10/31. doi: 10.1007/s00404-013-3064-9. PubMed PMID: 24170161.
[136] Chen C, Song X, Wei W, Zhong H, Dai J, Lan Z, et al. The microbiota continuum along the female reproductive tract and its relation to uterine-related diseases. Nat Commun. 2017;8(1):875. Epub 2017/10/19. doi: 10.1038/s41467-017-00901-0. PubMed PMID: 29042534; PubMed Central PMCID: PMCPMC5645390.
[137] Noyes N, Cho KC, Ravel J, Forney LJ, Abdo Z. Associations between sexual habits, menstrual hygiene practices, demographics and the vaginal microbiome as revealed by Bayesian network analysis. PLoS One. 2018;13(1):e0191625. Epub 2018/01/25. doi: 10.1371/journal.pone.0191625. PubMed PMID: 29364944; PubMed Central PMCID: PMCPMC5783405.
[138] Fettweis JM, Serrano MG, Brooks JP, Edwards DJ, Girerd PH, Parikh HI, et al. The vaginal microbiome and preterm birth. Nat Med. 2019;25(6):1012–21. https://doi.org/10.1038/s41591-019-0450-2. PubMed PMID: 31142849.
[139] Moumne O, Hampe ME, Montoya-Williams D, Carson TL, Neu J, Francois M, et al. Implications of the vaginal microbiome and potential restorative strategies on maternal health: a narrative review. J Perinat Med. 2021;49(4):402-11. Epub 2021/02/09. doi: 10.1515/jpm-2020-0367. PubMed PMID: 33554571.
[140] Redelinghuys MJ, Geldenhuys J, Jung H, Kock MM. Bacterial vaginosis: current diagnostic avenues and future opportunities. Front Cell Infect Microbiol. 2020;10:354. Epub 2020/08/28. doi: 10.3389/fcimb.2020.00354. PubMed PMID: 32850469; PubMed Central PMCID: PMCPMC7431474.
[141] Onderdonk AB, Delaney ML, Fichorova RN. The human microbiome during bacterial vaginosis. Clin Microbiol Rev. 2016;29(2):223-38. Epub 2016/02/13. doi: 10.1128/CMR.00075-15. PubMed PMID: 26864580; PubMed Central PMCID: PMCPMC4786887.
[142] Muzny CA, Blanchard E, Taylor CM, Aaron KJ, Talluri R, Griswold ME, et al. Identification of key bacteria involved in the induction of incident bacterial vaginosis: a prospective study. J Infect Dis. 2018;218(6):966-78. Epub 2018/05/03. doi: 10.1093/infdis/jiy243. PubMed PMID: 29718358; PubMed Central PMCID: PMCPMC6093354.
[143] Chandrashekhar P, Minooei F, Arreguin W, Masigol M, Steinbach-Rankins JM. Perspectives on existing and novel alternative intravaginal probiotic delivery methods in the context of bacterial vaginosis infection. AAPS J. 2021;23(3):66. Epub 2021/05/12. doi: 10.1208/s12248-021-00602-z. PubMed PMID: 33973067; PubMed Central PMCID: PMCPMC8356663.
[144] Husain S, Allotey J, Drymoussi Z, Wilks M, Fernandez-Felix BM, Whiley A, et al. Effects of oral probiotic supplements on vaginal microbiota during pregnancy: a randomised, double-blind, placebo-controlled trial with microbiome analysis. BJOG. 2020;127(2):275-84. Epub 2019/04/02. doi: 10.1111/1471-0528.15675. PubMed PMID: 30932317; PubMed Central PMCID: PMCPMC6973149.
[145] Zhang Y, Lyu J, Ge L, Huang L, Peng Z, Liang Y, et al. Probiotic *Lacticaseibacillus rhamnosus* GR-1 and *Limosilactobacillus reuteri* RC-14 as an adjunctive treatment for bacterial vaginosis do not increase the cure rate in a chinese cohort: A prospective, parallel-group, randomized, controlled study. Front Cell Infect Microbiol. 2021;11:669901. Epub 2021/07/24. doi: 10.3389/fcimb.2021.669901. PubMed PMID: 34295831; PubMed Central PMCID: PMCPMC8291149.
[146] Macklaim JM, Fernandes AD, Di Bella JM, Hammond JA, Reid G, Gloor GB. Comparative meta-RNA-seq of the vaginal microbiota and differential expression by *Lactobacillus iners* in health and dysbiosis. Microbiome. 2013;1(1):12. Epub 2014/01/24. doi: 10.1186/2049-2618-1-12. PubMed PMID: 24450540; PubMed Central PMCID: PMC3971606.
[147] de Vrese M, Laue C, Papazova E, Petricevic L, Schrezenmeir J. Impact of oral administration of four *Lactobacillus* strains on Nugent score - systematic review and meta-analysis. Benef Microbes. 2019;10(5):483-96. Epub 2019/04/24. doi: 10.3920/BM2018.0129. PubMed PMID: 31012733.
[148] van de Wijgert J, Verwijs MC. Lactobacilli-containing vaginal probiotics to cure or prevent bacterial or fungal vaginal dysbiosis: a systematic review and recommendations for future trial designs. BJOG. 2020;127(2):287-99. Epub 2019/07/13. doi: 10.1111/1471-0528.15870. PubMed PMID: 31299136.
[149] Zupancic S, Skrlec K, Kocbek P, Kristl J, Berlec A. Effects of electrospinning on the viability of ten species of lactic acid bacteria in poly(ethylene oxide) nanofibers. Pharmaceutics. 2019;11(9). Epub 2019/09/22. doi: 10.3390/pharmaceutics11090483. PubMed PMID: 31540399; PubMed Central PMCID: PMCPMC6781326.
[150] Ma B, Forney LJ, Ravel J. Vaginal microbiome: rethinking health and disease. Annu Rev Microbiol. 2012;66:371-89. Epub 2012/07/04. doi: 10.1146/annurev-micro-092611-150157. PubMed PMID: 22746335; PubMed Central PMCID: PMCPMC3780402.
[151] Gardner HL, Dukes CD. *Haemophilus vaginalis* vaginitis: a newly defined specific infection previously classified non-specific vaginitis. Am J Obstet Gynecol. 1955;69(5):962–76. Epub 1955/05/01 PubMed PMID: 14361525.
[152] DeLong K, Bensouda S, Zulfiqar F, Zierden HC, Hoang TM, Abraham AG, et al. Conceptual design of a universal donor screening approach for vaginal microbiota transplant. Front Cell Infect Microbiol. 2019;9:306. Epub 2019/09/27. doi: 10.3389/fcimb.2019.00306. PubMed PMID: 31555606; PubMed Central PMCID: PMCPMC6722226.
[153] Marrazzo JM, Antonio M, Agnew K, Hillier SL. Distribution of genital *Lactobacillus* strains shared by female sex partners. J Infect Dis. 2009;199(5):680-3. Epub 2009/02/10. doi: 10.1086/596632. PubMed PMID: 19199538; PubMed Central PMCID: PMCPMC3291173.
[154] Wilson BC, Butler EM, Grigg CP, Derraik JGB, Chiavaroli V, Walker N, et al. Oral administration of maternal vaginal microbes at birth to restore gut microbiome development in infants born by caesarean section: A pilot randomised placebo-controlled trial. EBioMedicine. 2021;69:103443. Epub 2021/06/30. doi: 10.1016/j.ebiom.2021.103443. PubMed PMID: 34186487; PubMed Central PMCID: PMCPMC8254083.
[155] Wampach L, Heintz-Buschart A, Fritz JV, Ramiro-Garcia J, Habier J, Herold M, et al. Birth mode is associated with earliest strain-conferred gut microbiome functions and immunostimulatory potential. Nat Commun. 2018;9(1):5091. Epub 2018/12/07. doi: 10.1038/s41467-018-07631-x. PubMed PMID: 30504906; PubMed Central PMCID: PMCPMC6269548.
[156] Chu DM, Ma J, Prince AL, Antony KM, Seferovic MD, Aagaard KM. Maturation of the infant microbiome community structure and function across multiple body sites and in relation to mode of delivery. Nat Med. 2017;23(3):314-26. Epub 2017/01/24. doi: 10.1038/nm.4272. PubMed PMID: 28112736; PubMed Central PMCID: PMCPMC5345907.
[157] Shao Y, Forster SC, Tsaliki E, Vervier K, Strang A, Simpson N, et al. Stunted microbiota and opportunistic pathogen colonization in caesarean-section birth. Nature. 2019;574(7776):117-21. Epub 2019/09/20. doi: 10.1038/s41586-019-1560-1. PubMed PMID: 31534227; PubMed Central PMCID: PMCPMC6894937.
[158] Miettinen R, Hermansson H, Merikukka M, Gissler M, Isolauri E. Mode of delivery–impact on risk of noncommunicable diseases. J Allergy Clin Immunol. 2015;136(5):1398-9. Epub 2015/07/08. doi: 10.1016/j.jaci.2015.05.032. PubMed PMID: 26148799.
[159] Mueller NT, Hourigan SK, Hoffmann DE, Levy L, von Rosenvinge EC, Chou B, et al. Bacterial baptism: scientific, medical, and regulatory issues raised by vaginal seeding of C-section-born babies. J Law Med Ethics. 2019;47(4):568-

78. Epub 2020/01/21. doi: 10.1177/1073110519897732. PubMed PMID: 31957590; PubMed Central PMCID: PMCPMC7908762.
[160] Neugent ML, Hulyalkar NV, Nguyen VH, Zimmern PE, De Nisco NJ. Advances in understanding the human urinary microbiome and Its potential role in urinary tract infection. mBio. 2020;11(2). Epub 2020/04/30. doi: 10.1128/mBio.00218-20. PubMed PMID: 32345639; PubMed Central PMCID: PMCPMC7188990.
[161] Finucane TE. "Urinary tract infection"-requiem for a heavyweight. J Am Geriatr Soc. 2017;65(8):1650-5. Epub 2017/05/26. doi: 10.1111/jgs.14907. PubMed PMID: 28542707.
[162] Stapleton AE, Au-Yeung M, Hooton TM, Fredricks DN, Roberts PL, Czaja CA, et al. Randomized, placebo-controlled phase 2 trial of a *Lactobacillus crispatus* probiotic given intravaginally for prevention of recurrent urinary tract infection. Clin Infect Dis. 2011;52(10):1212-7. Epub 2011/04/19. doi: 10.1093/cid/cir183. PubMed PMID: 21498386; PubMed Central PMCID: PMCPMC3079401.
[163] Sadahira T, Wada K, Araki M, Mitsuhata R, Yamamoto M, Maruyama Y, et al. Efficacy of *Lactobacillus* vaginal suppositories for the prevention of recurrent cystitis: A phase II clinical trial. Int J Urol. 2021;28(10):1026-31. Epub 2021/07/15. doi: 10.1111/iju.14636. PubMed PMID: 34258813.
[164] Tariq R, Pardi DS, Tosh PK, Walker RC, Razonable RR, Khanna S. Fecal microbiota transplantation for recurrent *Clostridium difficile* infection reduces recurrent urinary tract infection frequency. Clin Infect Dis. 2017;65(10):1745-7. Epub 2017/10/12. doi: 10.1093/cid/cix618. PubMed PMID: 29020210.
[165] Magruder M, Sholi AN, Gong C, Zhang L, Edusei E, Huang J, et al. Gut uropathogen abundance is a risk factor for development of bacteriuria and urinary tract infection. Nat Commun. 2019;10(1):5521. Epub 2019/12/05. doi: 10.1038/s41467-019-13467-w. PubMed PMID: 31797927; PubMed Central PMCID: PMCPMC6893017.
[166] Ahn J, Sinha R, Pei Z, Dominianni C, Wu J, Shi J, et al. Human gut microbiome and risk for colorectal cancer. J Natl Cancer Inst. 2013;105(24):1907-11. Epub 2013/12/10. doi: 10.1093/jnci/djt300. PubMed PMID: 24316595; PubMed Central PMCID: PMCPMC3866154.
[167] Wu N, Yang X, Zhang R, Li J, Xiao X, Hu Y, et al. Dysbiosis signature of fecal microbiota in colorectal cancer patients. Microb Ecol. 2013;66(2):462-70. Epub 2013/06/05. doi: 10.1007/s00248-013-0245-9. PubMed PMID: 23733170.
[168] Eslami SZ, Majidzadeh AK, Halvaei S, Babapirali F, Esmaeili R. Microbiome and breast cancer: new role for an ancient population. Front Oncol. 2020;10:120. Epub 2020/03/03. doi: 10.3389/fonc.2020.00120. PubMed PMID: 32117767; PubMed Central PMCID: PMCPMC7028701.
[169] Scheppach W, Bartram HP, Richter F. Role of short-chain fatty acids in the prevention of colorectal cancer. Eur J Cancer. 1995;31A(7-8):1077-80. Epub 1995/07/01. doi: 10.1016/0959-8049(95)00165-f. PubMed PMID: 7576995.
[170] Wang G, Yu Y, Wang YZ, Wang JJ, Guan R, Sun Y, et al. Role of SCFAs in gut microbiome and glycolysis for colorectal cancer therapy. J Cell Physiol. 2019;234(10):17023-49. Epub 2019/03/20. doi: 10.1002/jcp.28436. PubMed PMID: 30888065.
[171] Vital M, Howe AC, Tiedje JM. Revealing the bacterial butyrate synthesis pathways by analyzing (meta)genomic data. mBio. 2014;5(2):e00889. Epub 2014/04/24. doi: 10.1128/mBio.00889-14. PubMed PMID: 24757212; PubMed Central PMCID: PMCPMC3994512.
[172] Waldman AD, Fritz JM, Lenardo MJ. A guide to cancer immunotherapy: from T cell basic science to clinical practice. Nat Rev Immunol. 2020;20(11):651-68. Epub 2020/05/21. doi: 10.1038/s41577-020-0306-5. PubMed PMID: 32433532; PubMed Central PMCID: PMCPMC7238960.
[173] Martins F, Sofiya L, Sykiotis GP, Lamine F, Maillard M, Fraga M, et al. Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. Nat Rev Clin Oncol. 2019;16(9):563-80. Epub 2019/05/17. doi: 10.1038/s41571-019-0218-0. PubMed PMID: 31092901.
[174] Helmink BA, Khan MAW, Hermann A, Gopalakrishnan V, Wargo JA. The microbiome, cancer, and cancer therapy. Nat Med. 2019;25(3):377-88. Epub 2019/03/08. doi: 10.1038/s41591-019-0377-7. PubMed PMID: 30842679.
[175] Elkrief A, Derosa L, Zitvogel L, Kroemer G, Routy B. The intimate relationship between gut microbiota and cancer immunotherapy. Gut Microbes. 2019;10(3):424-8. Epub 2018/10/20. doi: 10.1080/19490976.2018.1527167. PubMed PMID: 30339501; PubMed Central PMCID: PMCPMC6546322.
[176] Gopalakrishnan V, Spencer CN, Nezi L, Reuben A, Andrews MC, Karpinets TV, et al. Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. Science. 2018;359(6371):97-103. Epub 2017/11/04. doi: 10.1126/science.aan4236. PubMed PMID: 29097493; PubMed Central PMCID: PMCPMC5827966.
[177] Ahmed J, Kumar A, Parikh K, Anwar A, Knoll BM, Puccio C, et al. Use of broad-spectrum antibiotics impacts outcome in patients treated with immune checkpoint inhibitors. Oncoimmunology. 2018;7(11):e1507670. Epub 2018/11/01. doi: 10.1080/2162402X.2018.1507670. PubMed PMID: 30377571; PubMed Central PMCID: PMCPMC6205076.
[178] Huemer F, Rinnerthaler G, Westphal T, Hackl H, Hutarew G, Gampenrieder SP, et al. Impact of antibiotic treatment on immune-checkpoint blockade efficacy in advanced non-squamous non-small cell lung cancer. Oncotarget. 2018;9(23):16512-20. Epub 2018/04/18. doi: 10.18632/oncotarget.24751. PubMed PMID: 29662663; PubMed Central PMCID: PMCPMC5893258.
[179] Sen S, Carmagnani Pestana R, Hess K, Viola GM, Subbiah V. Impact of antibiotic use on survival in patients with advanced cancers treated on immune checkpoint inhibitor phase I clinical trials. Ann Oncol. 2018;29(12):2396-8. Epub 2018/10/12. doi: 10.1093/annonc/mdy453. PubMed PMID: 30307530; PubMed Central PMCID: PMCPMC6311953.
[180] Taur Y, Coyte K, Schluter J, Robilotti E, Figueroa C, Gjonbalaj M, et al. Reconstitution of the gut microbiota of antibiotic-treated patients by autologous fecal microbiota transplant. Sci Transl Med. 2018;10(460). https://doi.org/10.1126/scitranslmed.aap9489. PubMed PMID: 30257956.
[181] Davar D, Dzutsev AK, McCulloch JA, Rodrigues RR, Chauvin JM, Morrison RM, et al. Fecal microbiota transplant overcomes resistance to anti-PD-1 therapy in melanoma patients. Science. 2021;371(6529):595-602. Epub 2021/02/06. doi: 10.1126/science.abf3363. PubMed PMID: 33542131; PubMed Central PMCID: PMCPMC8097968.