*Supplement Article*

# Personalized Nutrition Through The Gut Microbiota: Current Insights And Future Perspectives

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*This narrative review discusses how to preserve or increase health through personalized nutritional products and services using microbiome data. In contrast to other reviews, which discuss this subject in the light of metabolic disorders and/or with a nutrition-affects-the-microbiota view, this review takes the perspective that the gut microbiota (GM) affects nutrition. Gut microbes affect host nutritional status through their role in energy harvest and nutrient availability. Consequently, GM modulation could contribute to fulfil nutritional requirements and in this way conquer malnutrition and disease. This review provides an overview of microbiota modulation methods that could be used to improve nutritional status as well as the personalization of these approaches. While some of these methods are immediately applicable, others require more development to assess their feasibility and safety.*



## INTRODUCTION

The overall goal of personalized nutrition is to preserve or increase health using relevant information about the individual to deliver personalized nutritional products and services. The idea that individualizing nutritional advice, products, or services will be more effective than more generic approaches is based on 2 main observations, namely: 1) differential responses to foods/nutrients are dependent on genotypic or phenotypic characteristics, and 2) differential responses in eating behavior are dependent on personal preferences, barriers, and objectives.[1] This review connects personalized nutrition to the gut microbiota (GM), the ecological community of microorganisms residing in the gastrointestinal tract (see graphical summary).[2]

Several facts warrant the inclusion of GM data in personalized nutrition. First, the GM influences host nutritional status and phenotype. In both over- and under-nutrition there is substantial evidence that the GM plays a role in regulating nutrient absorption and storage.[3,4] Second, the outcome of a nutritional intervention might depend on the host-associated GM. Zeevi et al[5] showed that GM composition and function were partly responsible for the marked inter-individual variability in postprandial glycemic responses to identical meals. Furthermore, studies on the efficacy of non-caloric artificial sweeteners for weight-loss demonstrate mixed and conflicting results, which could be partly reconciled by the GM mediating the effects of the non-caloric artificial sweeteners on metabolism.[6] Similar evidence has been gathered within the atherosclerosis field, where some microbiome configurations seem to be better suited to carry out the conversion of L-carnitine, found abundantly in red meat, to the pro-atherogenic compound trimethylamine-N-oxide.[7]This suggests that

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*Key words: Colon, Human; Designer Probiotics; Energy Extraction; Food Availability; Gastrointestinal Tract; Gut Microbiota; In Situ Microbiome Modulation; Metabolites; Microbiome; Mineral Absorption; Minerals; Next-generation Probiotics; Personalized Nutrition; Prebiotics; Precision Nutrition; Probiotics; Short Chain Fatty Acids; Synbiotics; Urea Salvage; Vitamin Production and Absorption*



doi: 10.1093/nutrit/nuaa098

general recommendations (eg, low-glycemic response diets, use of non-caloric artificial sweeteners to reduce caloric consumption, and reduced red meat intake to prevent atherosclerosis) may not be suitable or may even be harmful to certain population subsets and that recommendations should be personalized according to an individual's microbiome.[8] Third, the nutritional value of food depends on the GM. Contrary to what nutritional labels indicate, the amount of calories and nutritional elements that are available to the human body is not a fixed number applicable in every situation or for each person. The energy and nutrients humans are able to extract from food depends on factors like preparation methods (eg, cooking),[9] oral processing (eg, chewing), genetic polymorphisms (eg, composition of digestive fluids, absorption mechanisms),[10] and, importantly, GM composition and function. The GM aids with energy extraction through short-chain fatty acid production and urea recycling.[11,12] Moreover, the GM is an additional source of essential nutrients through the production of vitamins[13,14] and its influence on mineral absorption.[15–17] The GM could be integrated into personalized nutrition by using it as a biomarker to predict and/or follow-up on the responsiveness to dietary components and interventions. Current reviews focus almost exclusively on this application and this option will therefore not be discussed here. Extensive reviews on the subject are provided by Mills et al[18]; de Toro-Martin et al[19] and Jin et al[20] Within the literature, the option of steering the GM toward a healthier composition through nutritional interventions has also been raised.[19,21] What exactly constitutes a healthy GM, however, remains unclear.[22] Options of steering the GM toward a healthier composition would encompass both interventions aimed at general objectives, such as increasing diversity, or at specific microbes, such as steering the GM toward the production of certain signaling metabolites. Although the nutritional advice/product/service would in this case indirectly serve the goal of a better health status, namely through GM modulation, this also falls under personalized nutrition. Such approaches are reviewed in Mills et al[21] and de Toro-Martin et al[19]. Another way in which personalized nutrition could embrace the advancements made within the GM field is by modulating an individual's GM to improve the nutritional or metabolic status. Here, this last option will be further discussed, with a focus on nutritional status (Figure 1).[18–20]

## RELEVANCE OF MODULATING THE GUT MICROBIOME FOR NUTRITIONAL PURPOSES

Modulating the GM to efficiently use the available food and achieve a better nutritional status, eg, extracting more nitrogen, energy, minerals or vitamins, is relevant today in several aspects. First, in situations of reduced or altered food intake, it could prevent looming undernutrition and, in more extreme cases, protect individuals from developing severe acute malnutrition. Agricultural losses due to extreme weather conditions, ever more common in the last several years due to climate change, pose a threat to farmers all over the world, and may compromise the food supply. A GM modulated for high nutritional efficiency could partially buffer the acute nutritional stresses of famine that accompany such losses in vulnerable populations. In addition, it could prevent the development of deficiencies in situations where malnutrition is a more chronic condition. According to the World Health Organization, approximately 462 million adults are currently underweight, while 224 million children under 5 years are wasted or stunted because of malnutrition.[23] Adequate nutrition is of utmost importance during pregnancy and early childhood for the development of several organs, including the brain. Malnutrition of the mother or child has lifelong, often severe, effects.[24] Every improvement in nutritional status accomplished during this period is valuable, as it will put the affected children on a better life track. If the necessary food sources are actually available but their consumption is reduced for financial reasons, as might be the case in low-income countries, simply providing the food is likely a more cost-effective solution. A GM modulation strategy would, however, also be useful in less extreme cases, namely by aiding the transition to other food sources. A change toward a diet in which the required nutrients are less readily available may be necessary for a variety of reasons. One would be the introduction of new crops or other varieties, driven by innovations or the need for resistance to extreme weather conditions. Another would be the transition to a more plant-based diet, which is currently under way in several western countries due to a greater acknowledgement of the impact of meat consumption on health and environment, as well as animal welfare. For whatever reason dietary changes in this direction occur, the human GM might not be ideally adapted to aid with the digestion of this altered diet. Modern human beings might have lost the necessary microbes and/or functions during recent evolution. Indeed, modern human lifestyle probably has disturbed the human-microbe relations forged throughout their symbiotic history. Cooking practices, decreased fiber consumption, increased hygiene, and medication use have greatly reduced the diversity as well as functional capacity of the human GM in western societies. People living in more remote communities or with a hunter-gatherer lifestyle consistently show greater species richness and increased capacity for carbohydrate degradation. Wild-living primates, who

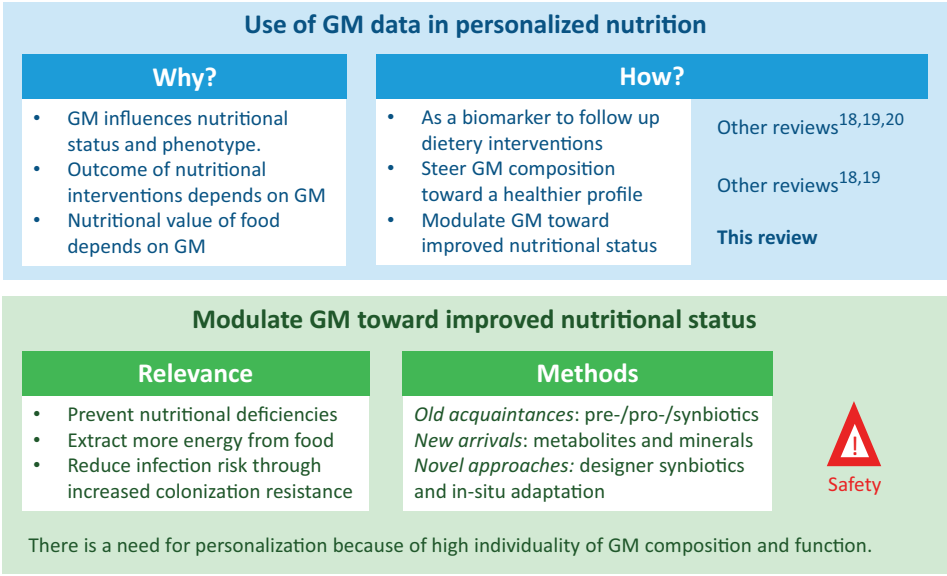


*Figure 1:* Graphical summary of this review.

consume a large variety of plants, devoid of any preparation, show even larger deviations in these parameters.[25] This suggests that *homo sapiens* are rapidly losing microbial species and functions.[26] Restoring these through GM modulation might thus lead to a broader fermentation capacity and in this way contribute to increased availability of nutrients for the host.

GM modulation toward increased nutritional efficiency could also improve host health in situations where nutrients are not limited. For example, GM modulation could be beneficial for treating iron deficiency, the most prevalent micronutrient deficiency worldwide. Iron deficiency contributes to multiple pathologies, especially during pregnancy, through direct effects on the formation and function of organs, most importantly the brain. This can be partly solved by iron supplementation, but there is strong evidence that supplemental iron given in non-physiological amounts increases the risk for bacterial and protozoal infections, especially malaria, in susceptible populations of iron-depleted individuals.[27,28] GM modulation toward increased iron absorption could partly replace iron supplementation, and reduce the associated risks. Similarly, modulating the GM toward increased calcium absorption could be a way to prevent bone diseases such as osteoporosis. Pre- and probiotics influence bone density and health, most probably due to effects on calcium absorption.[16,29] GM modulation toward increased calcium absorption could thus complement supplementation. On the other side, modulation toward increased nitrogen extraction would allow for lower protein consumption, which might be beneficial in several disease settings, including kidney disease.[30] In essence, more efficient use of every nutrient would reduce the required intake levels of those nutrients. Although this might be undesirable for gastronomists, it could offer substantial benefits from biological, economical, and other perspectives.

Lastly, the efficient use of the colonic nutrient flow by the GM enhances colonization resistance, reducing the chance for pathogens to establish a full-blown infection.[31,32] One of the most determining factors for colonization success is competition for resources. According to the nutrient-niche hypothesis, an organism must use at least 1 limiting nutrient better than all the resident microbes in order to successfully colonize the host. The aggregate capacity of the native microbiota to consume the nutrients required by the pathogen thus determines the outcome of a challenge.[31–33] Consequently, large gaps between colonic nutrient flow and fermentation capacity leave the door wide open for infections. Extending the digestive functions of the GM could fill this gap and close the door.

GM modulations increasing nutritional status could thus lead to the improvement of general health as well as protection against disease (eg, infections and severe acute malnutrition).

## WHY PERSONALIZE?

Reaching stable GM modulation, whatever the underlying goal, is not straightforward. First, the high individuality of GM composition and, although less so, function, should be considered.[34–36] Of the 664 genera revealed in a combined cohort of more than 3000 people, only 14 genera were present in 95% of the people.[35] Despite conservation at the highest taxonomic ranks, the composition of the adult gut microbiota varies dramatically from person to person, with large differences

in the presence as well as the relative and absolute numbers of genera and species.[34,35,37,38] Because composition partly determines function, this also means functional capacity differs among populations and individuals. As there are large discrepancies in presence-absence profiles, some individuals might already have the necessary community of species to perform the desired function, while others might lack them completely. Differences in total abundance of those species further differentiate functional capacities between individuals. Hence, to extend the GM enzymatic pool of an individual, different genes/species will need to be introduced for each person. For example, the GM of some Japanese individuals has the ability to degrade the polysaccharide porphyran found in seaweed, a common constituent of Japanese cuisine. The carbohydrate-active enzymes involved in this degradation process migrated from a marine bacterium to 1 GM member. Colonic fermentation of porphyran leads to oligosaccharides providing energy for both the resident microbes as well as the host. Yet, for those who do not possess this specific bacterium porphyran is just another fiber.[40] To enhance the functional capacities of the residing or introduced bacteria, compositional changes towards increased abundance of the potent strains could be an option. Therefore, a personalized approach, in which an individual's microbiome is screened to determine the presence and abundance of functions, allows for a more precise characterization of the needs as well as a more detailed follow-up of progression.

Another reason to work toward personalized modulation is that the success of strain engraftment or enhancement will depend on the personal GM setting. The highly personal compositional 'starting conditions' determine the outcome of interventions through priority effects.[39] The practice of fecal material transfer (FMT), in which a donor's GM is transplanted into a recipient's gut, shows largely diverging results.[41,42] Some patients partially 'accept' the donors GM, others do not or shift back to their previous constellation after some time. Whether or not the disease is (temporarily) cured through FMT seems to depend on both the donor's and recipient's microbiome. It has been suggested that a kind of 'match' is required, but the rules of the matchmaking have not yet been derived from these studies. Probably, host-selection and colonization resistance, among other factors, determine the outcome of scattergun approaches like FMT. For clinical researchers it is clear that 1 size does not fit all for microbiome modulation.[41,42] Hence, personalization of the treatments is a way forward. There is no reason why microbiome modulations for precision nutrition should be any different. In addition to enhancing treatment success, personalized methods could also reduce the unintentional elimination of a host-adapted, resident microbiota in cases where this is undesirable (eg, healthy individuals). To summarize: The unique symbiotic community that we constitute calls for a unique, personalized approach.

## PERSONALIZED GUT MICROBIOTA MODULATION METHODS

A range of methods can be applied (synergistically) to obtain the goal of personalized nutrition through microbiome modulation. First, there are the old acquaintances within the current probiotics, prebiotics, fibers, and synbiotics that could be targeted more specifically. Second, new arrivals of the old ways, such as next-generation/novel probiotics, or new prebiotics and synbiotics, as well as radical innovative methods, can extend the current working area.

### Old acquaintances: Probiotics, prebiotics, and synbiotics

Probiotics are defined as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host".[43,44] Current probiotics include only a limited number of genera, mostly belonging to the Lactobacilli and Bifidobacteria families.[2] Initially identified in the gut or in fermented food products (eg, yogurt, kefir, pickles) and further isolated, grown, tested, and exploited by the food industry, these organisms have a long history of safe use. Commonly exploited species have a Generally Regarded as Safe status in the United States, or have been granted Qualified Presumption of Safety status by the European Food Safety Authority.[43,44] Some of these strains have been studied and applied for specific nutritional purposes, such as increased production of short-chain fatty acids within the host gut or vitamin production within food products (reviewed in Leblanc et al[45]). In recent years, improved sequencing and culturing techniques have led to the identification of species not belonging to the families found within the traditional probiotics used today, that could also 'confer a health benefit on the host', the so-called next-generation probiotics. At the moment, investigated next-generation probiotics strains (eg, *Bacteroides*, *Clostridium*, *Faecalibacterium*, and *Akkermansia*) are selected based on their association with health in disease studies.[44,46] Selection based on criteria serving pure nutritional purposes is uncommon.

Prebiotics were originally defined as" non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a

limited number of bacteria in the colon, and thus improves health".[47] Currently, this definition is somewhat debated, with suggested amendments proposing the extension of the concept to other body sites (eg, the small intestine) as well as the inclusion of benefits on host wellbeing (eg, improved transit, reduced bloating). Although the concept emerged from observations of selective stimulation of *Bifidobacterium* growth with inulin supplementation, removal of the selectivity restriction has been proposed as well.[47] With the possibility of assessing the complete microbial community through (amplicon-) sequencing, several recent mouse studies have shown a broad-spectrum response of the gut microbial community following stimulation with known prebiotic compounds.[47] Similar studies in humans, however, have confirmed the selectivity of current prebiotics in a human setting.[48–50] In 2016, the International Scientific Association for Probiotics and Prebiotics proposed a revision of the definition to" a substrate that is selectively utilized by host microorganisms conferring a health benefit".[51] This definition expands the concept to include non-carbohydrate substances and environments other than the colon for the selective stimulation to take place.[51] Here, the term prebiotic is used according to this updated definition. Currently, widely used prebiotics include fructo-oligosaccharides, galacto-oligosaccharides, xylo-oligosaccharides, and inulin.

Synbiotics refer to food ingredients or dietary supplements combining probiotics and prebiotics in a form of synergism, hence synbiotics.[52] For example, the prebiotic inulin together with a probiotic inulin-fermenting *Bifidobacterium* strain would be a synbiotic. Synergy is important within this definition, so that the simultaneous use of a pre- and probiotic that work independently cannot be considered synbiotics, as recommended by the United Nations Food & Agriculture Organization.[53]

Precision nutrition using the current pro/pre/synbiotics is possible through the selection of susceptible sub-groups that would benefit from an intervention. At this moment, such a selection is still quite challenging due to the lack of targeted studies including microbiome data. As microbiome screening is becoming ever more affordable, however, this will likely change soon. While probiotics do not necessarily need to colonize the gut for some applications, eg, only the purified membrane protein of *Akkermansia* is sufficient to improve metabolism in obese and diabetic mice,[54] this is a necessary requirement for changes in nutritional status as discussed above. Microbiome screening could not only select those that might benefit from the pro/pre/synbiotic application, but also provide the necessary information to predict the colonization efficiency of probiotic strains and predict the stimulation potential of prebiotic compounds according to an individual's microbiota composition and function. Indeed, colonization efficiency is highly personal and depends on an individual's GM composition and function, eg, strains occupying the same nutritional niche will have less chance to stably colonize given the high competition for resources. Similarly, prebiotic stimulation stands or falls with the presence and even abundance of the target bacteria,[51] which can vary largely between persons[34,35] and, when considering abundance, also in time.[55–57] Future pro- and prebiotic intervention studies including microbiome data should therefore adopt a set-up that allows for such predictive analysis (eg, including a baseline sample and assessing the strain engraftment/viability of the probiotic strain). The same holds for next-generation pro/pre/synbiotics, as they are based on the same principles. Health benefits of current and next-generation probiotics range widely, but do not often comprise pure nutritional gains. To modulate the microbiome as outlined above, researchers will need to identify new probiotic strains. Importantly, this identification needs to be tailored to the individual. Indeed, what might be a probiotic strain for 1 person, might not be for the other. Several options exist to increase nutrient extraction from food through probiotics. For example, improve the usage of compounds an individual is not or sub-optimally using, eg, colonic secreted urea or certain types of carbohydrates, or re-introducing the degradation capacities lost during recent evolution. Finally, it is not unthinkable to extend the functional capacities of the GM with completely new functions, opening up a new range of nutritionally valuable food products. Where to look for such probiotic strains? A first source would be the data already gathered in previous studies. Obviously, those studies characterizing the functional capacity of the human GM and identifying nutritionally valuable enzymatic activity could be mined, but alternatively also the metagenomic data gathered by studies with unrelated aims. Public databases now contain GM reference genome sets of substantial size ($>1500$[58], $>1900$[59]), extensive catalogs of GM reference genes ($\pm 10$ million[60]), and metagenomic data sets with an ever-increasing number of fecal samples ($>1200$[60], 3800[61]). Comparing an individual's functional profile against the combined functional profile of thousands of individuals would reveal the gaps and suggest possible probiotic options. Secondly, the chances of detecting strains/functions lost throughout evolution could be increased by sampling from those that might have retained them. Possible sources include the guts of vegetarians, who generally consume more plants and might therefore have larger carbohydrate-fermentation capacities; or hunter-gatherer populations, who might harbor different and more diverse GM than industrialized individuals, making these biomes interesting for

the discovery of new probiotic strains. In 2018, the initiative Microbiome Search Engine[62] was launched, assessing the similarity of a new set of microbiome samples against all those collected previously in other studies using a database with 16S amplicon sequencing data. Since then, researchers are able to check the novelty of microbiome samples (how different are they from what has already been sequenced?), and the study effort already devoted to them (how many close neighbors of this sample already exist?). In this way, researchers can identify gaps in sampling effort and act accordingly. In time, such search engines could be extended to also address metagenomes, allowing for the assessment of novelty on a functional level. Although human-associated organisms are more likely to result in stable, health-promoting symbioses, given the shared history, other sources might deliver candidates that are even more interesting. Primates, with their diverse diet devoid of cooking practices would likely be a good source for the discovery of plant-degrading functions. Ruminants are probably the ideal source to find specialized urea-degraders. Algae and marine bacteria associated with seaweed might be able to degrade complex seaweed polysaccharides. In summary, to discover organisms able to assist in the degradation of specific compounds, we need to sample the environments that are likely to have evolved such functionalities.

In addition to new probiotics, the use of new prebiotics could also help obtain GM modulation. As a side note, several of the most widely used prebiotics, such as fructo-oligosaccharides, galacto-oligosaccharides, and inulin, have been shown to have a specific effect on bacterial groups other than Lactobacilli and Bifidobacteria (eg, *F. prausnitzii, Anaerostipes*), in ecosystem-wide studies, which indicates their modulation potential might be more extensive then previously thought.[50,51,63] Other oligosaccharides, such as xylo-oligosaccharides, arabinoxylan, pectin-oligosaccharides, isomalto oligosaccharides, and human milk oligosaccharide have also shown beneficial and selective effects. The same seems to apply for resistant starch, a form of starch that cannot be degraded in the small intestine, and polyphenols, a broad category of secondary plant metabolites. All of these compounds are extensively reviewed in Lordan et al[51] To find new prebiotics, a similar strategy as for probiotics can be applied. This approach becomes even more relevant in the case of synbiotics.

## New arrivals: Metabolites and minerals

Besides the traditional methods (pro/pre/synbiotics), applied after microbiome screening and evaluation, several other options could steer the microbiome in a more precise, personal way. The use of gut metabolites as modulators is 1 option. Supplementation with lactate or acetate could aid the stimulation of butyrate-producing bacteria, as shown by several studies,[51] while host mucus components could stimulate mucus degraders such as *Akkermansia municiphila*.[64] While the metabolites in the former example are quite broadly consumed, some, like those of the latter example, might be specific for a limited number of bacteria. Some metabolites would thus fall within the prebiotics category, according to the updated definition. These GM modulations should however be informed by the use of computational modeling to elucidate the metabolic functions of the species present within an individual's gut, to predict possible substrates, the effects of supplementing them, and the need to compliment this approach with probiotics. The data and methods needed to do so might not be fully available at this moment, but will be in the near future. At this moment, the most convenient way to map sequenced genes or organisms onto metabolic networks is through the Kyoto Encyclopedia of Genes and Genomes. As this approach might lack some specificity (eg, the presence of non-bacterial pathways or strictly aerobic reactions), however, several gut-bacteria specific approaches have been developed that constrain the amount of possible pathways in accordance with knowledge about the gut environment and curating pathways through literature review and experimental data. An *Akkermansia muciniphila*-specific model, developed by Willem De Vos's group, showed this bacterium's preferential mucin-degrading lifestyle and aided in the design of a minimal medium for its cultivation.[64,65] A few years ago, Jeroen Raes's lab developed a gut-specific metabolic module set and complementing analysis frame work called Gomixer (available at: Http://www.raeslab.org/gomixer/) for predicting the metabolic capacity of complete communities based on metagenomic data. Recently, Ines Thiele's group presented the curated metabolic reconstructions of 773 members of the human GM using their AGORA framework.[66] Despite the considerable work needed to develop such frameworks, other groups will likely take up similar initiatives, further expanding the knowledge on metabolic capacity of human GM and, in time, allow for personalized applications.

Another option is the use of minerals. Minerals, such as iron, magnesium, sodium, and calcium, are essential elements for living organisms, including most bacteria, and therefore likely have an effect on the composition of the GM.[51] Studies show that iron has an adverse effect on the GM. It decreases butyrate production and leads to the expansion of pathogenic bacteria, possibly related to the production of siderophores. While there are some insights to suggest that

other minerals, such as zinc, can have an impact on the GM, little is currently known.[51]

### Novel approaches: Designer probiotics or in situ adaptation

More futuristic options include the use of designer probiotics as well as methods to adapt the residing bacteria *in situ*. The first concept, mainly discussed within the context of therapeutics, is not yet well defined. Here, designer probiotics are defined as genetically modified microorganisms that, when administered in adequate amounts, confer a health benefit on the host. Within the field of precision nutrition, designer probiotics could cover a range of applications. They could be used to extend the functional profile of the GM regarding nutritional goals after microbiome screening. Current probiotics could be adapted to perform a function of nutritional importance that is lacking. In this way, the advantages of current probiotics – their own health benefits as well as the knowledge gathered about their safety - could be combined with those of strains from other environments. One step further in personalization would be to create designer probiotics already adapted to the host environment by manipulating a person's own GM, given that its members can be cultured and manipulated. If the added function provides a competitive advantage, introducing such a modified strain could lead to the establishment of this strain within the gut environment through competition. Odds et al[67] showed a pathogenic strain of *Candida albicans* outcompeted a previously acquired strain after a new hospital admission. Recently, the Sonnenburg group actually modified a commensal *Bacteroides* strain to carry the highly specific porphyran-degradation gene cluster and showed it was able to outcompete the original *Bacteroides* strain in mice under a continuous supply of porphyran.[68] In this regard, it is worth pointing out that nutritional adaptations could also enhance the success and safety of therapeutic designer probiotics. By using the porphyran-degradation gene set, Sonnenburg's team showed that exogenous strain engraftment is possible over a range of different background microbiota constellations by creating an exclusive metabolic niche.[68] They were able to fine-tune the abundance of the colonizer by varying porphyran dosage. In this way, therapeutic designer probiotics could thus be applied reversibly, enhancing their colonization changes at first and decreasing their competitive advantage later in case their presence is no longer providing benefits.[68] Another option to introduce additional functionality but circumvent the difficulties of colonization and host adaptation is to modify the residing bacteria *in situ*. Harris Wang's group recently reported a method, metagenomic alteration of gut microbiome by in situ conjugation, to genetically modify gut microbiota in their native habitat by engineering the mobilome—the repertoire of mobile genetic elements in the gut microbiome.[69] Using their method within the mouse gut, they were able to modify a diverse range of bacteria with their designed plasmids, spanning approximately 19 genera across 4 phyla. Trans-conjugants constituted approximately 5% of the total microbiota within 6 h after introducing the donor strain. Unless the genetic payload got integrated within the microbial host genome, however, the introduced genetic material disappeared from the microbial population within 72 h.[69] Their work provides a proof of principle, but more research is required to allow for better quantitative and temporal control of genetic-payload retention, and to assess the safety of such approaches. Finally, yet importantly, an approach based on augmenting instead of reducing randomness might be useful in some occasions. The idea is that instead of turning the scattergun into a sniper rifle to obtain personalized microbiome modulation, scattergun munition could be increased. In other words, rather than selecting a specific set of bacteria upfront of admission, based on knowledge gathered through research and screening, a diverse range of bacteria could be offered, after which nature performs the selection. For some purposes, like increasing diversity in composition and function, or 'reshuffling a dysbiotic system', this might well be the easiest solution. The idea is that randomness is an inherent characteristic of the gut microbial system and that instead of trying to induce an artificial –more beneficial– order, re-disordering might work just as well or even better.[42] Shotgun munition can be increased in different ways, depending on the purpose or application. The nutritional goals as discussed above could be achieved by using mixtures of probiotics instead of single strains or simply by increasing the intake and diversity of naturally-occurring microbes through the consumption of a more diverse range of food products, cultured, and processed without disruptive treatments.

## SAFETY AND SUCCESS OF PERSONALIZED GM MODULATION

Personalized GM modulation can be achieved in various ways. The safety and success rates are 2 important points to consider for all these options. Before wide adoption of personalized microbiome modulations is possible, clinical or scientific studies need to demonstrate their efficacy and safety. At this time, such studies are scarce and several challenges compromise their set-up and execution. In addition to the limitations regarding compositional and functional microbiota screening

(eg, unknowns in functional datasets, shortage of appropriate functional models, and high sequencing costs), there is a general lack of experience regarding study design and statistical analysis for precision medicine. The development of methods to assess the value of personalized approaches is proceeding slowly, partly because of the focus on discovery as opposed to confirmatory research.[70] Advancements within other precision medicine domains, however, are likely to stimulate development and discovery within the microbiome field. Although several methods could readily enter such trials, others do not yet allow for the ideally desired control to reduce the risk of adverse events. Indeed, researchers can never fully predict the outcome of an intervention with biotherapeutics, given the complex interactions with the microbiota and the host. The degree of risk, however, can certainly vary. The age-long experience with pro- and prebiotics warrants less concern than more recently used or developed methods. In general, current pro/pre/synbiotics are considered safe, but side notes regarding antibiotic resistance can be made (for a review regarding the safety of next-generation pro/pre/synbiotics see Saarela[43]). New strains or molecules do not necessarily carry more risk, but need to be well characterized and tested. Designer pro- or synbiotics could not only have unexpected bad consequences in the target population, but their transfer to other persons and/or the environment might also be problematic. Moreover, approaches based on uncharacterized mixtures and selection by the host are inherently risky. Nevertheless, such approaches, namely FMT, are being regularly applied in the treatment of *Clostridium difficile* infections, and inflammatory bowel diseases. The severity of these conditions can partly justify the risks taken. Yet, FMT has also been applied within less severe gastrointestinal conditions, such as irritable bowel syndrome, and syndromes with limited evidence for gastrointestinal or microbial causative agents, such as autism. Microbiome modulation toward nutritional efficiency is further along the health spectrum and such approaches should thus require considerable evidence of benefits and safety before application. Despite their obvious advantages, methods to adapt the microbiome in situ are not yet beyond the proof of concept stage. A good understanding of the adaptive capacities of the microbiome (eg, through horizontal gene transfer) and the role of selection in that process, from strain to holobiont level,[69,71,72] is currently lacking. Answering such questions will allow these methods to be adapted to increase safety and success, and pave the way for the assessment of their applicability in a range of settings, including the nutritional sciences.

## CONCLUSION

The GM plays an important role in the nutritional status of its host. GM modulation could improve the efficiency of nutrient extraction and by doing so, improve general health and conquer malnutrition and disease. Given the high individuality of GM composition and function, 1-size-fits-all approaches are limited and personalization will be necessary. Personalized GM modulation for nutritional purposes can be achieved by combining long-known methods such as pro/pre/synbiotics as well as newly developed approaches with microbiome screening and subsequent personalization. While some approaches can be readily applied, others will need more development and testing to assess their feasibility and safety. Given the potential personal and/or community-wide negative outcomes, safety is paramount in the development and application of personalized microbiome interventions.


### Acknowledgements

I would like to thank Astrid Vermeulen, Erik Bootsma, and Marie Joossens for valuable feedback on the first version of this manuscript, as well as all members of the Jeroen Raes and Ilana Brito labs for the insightful discussions throughout my research career that have shaped my view and allowed me to fall back on a broad knowledge base when writing this review.

## FUNDING AND SPONSORSHIP

The author acknowledges funding from Fonds Wetenschappelijk Onderzoek Vlaanderen (FWO), grant number 12Q8919N, and the European Union's Horizon 2020 research and innovation programme under the Marie Skodowska Curie grant agreement No 895167. The author received travel support to present this material at the 8th International Conference on Nutrition and Aging, October 2019, Tokyo, Japan.

*Declaration of interest:* No conflict of interests to declare.


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