Perspective

Gut Microbiota-Informed Precision Nutrition in the Generally Healthy Individual: Are We There Yet?

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Running title = Microbiota and Precision Nutrition in the Healthy

Potential conflicts of interest = BN, GB, and MJ are employees of InsideTracker. JB serves on the Scientific Advisory Board.

Sources of support: InsideTracker is the sole funding source.

Data sharing = There are no data to share from this perspective article.
Abstract

Since next generation sequencing facilitated high-throughput and cost-efficient genomics analyses, the human gut metagenome has become an emerging frontier to explore toward precision nutrition. Significant progress has been made in identifying gut microbial features associated with a wide spectrum of human disease. However, other than a few microbiome-disease relationships, there is a dearth of confirmed causal inferences, particularly in generally healthy populations. The relatively high unexplained variability in microbiome compositions in this group warrants caution in applying this complex biomarker toward precision nutrition, as our understanding of what constitutes a healthy microbiome is still rudimentary. While gut microbiota harbor integrated environmental and host-specific information with the potential to facilitate personalized nutritional and lifestyle advice, these data cannot yet be confidently interpreted toward precise recommendations. Thus, nutritional advice for generally healthy individuals based on personal microbiome composition analysis may not yet be appropriate unless accompanied by established blood and physiological biomarkers.

Keywords: microbiome, precision nutrition, blood biomarkers, nutrigenomics, generally healthy

Summary

Gut microbiome composition analysis can offer deep layers of health data, but these insights are not yet useful toward precision nutrition for generally healthy individuals.

Introduction

No longer in its infancy, gut microbiome research is producing insightful results ripe for evaluation toward application to precision nutrition. However, the factors that contribute to a healthy (or unhealthy) state of the intestinal microbiota are dauntingly complex: an interplay of genetic, environmental, clinical, and stochastic inputs that can result in two seemingly healthy individuals'
microbiomes to have almost nothing in common from a taxonomical standpoint (1). While we now have at our disposal a plethora of microbiome-disease association data, there is a need to establish cause-and-effect relationships via large-scale longitudinal studies where the initial healthy human microbiome state is functionally characterized and subsequently challenged with interventions whose effects on host microbiota and physiology can then be interrogated for molecular mechanisms. While evaluating whether our current understanding of the microbiome affords us the ability to make microbiome composition-based dietary and lifestyle recommendations, it is worthwhile considering some of the confounding factors that play a role in the variation of the microbiome between individuals. These confounders can significantly impact the utility of microbiome characterization toward iterative health optimization at the level of the generally healthy individual.

Although this field has progressed exponentially toward more granular datasets, replication of bacterial species-level associations with host phenotypes is scarce, with the most promising reports correlating these associations with easily measured blood biomarkers or phenotypes. Thus, current gut microbial signatures may be just another, albeit highly elaborate, proxy for causal mechanisms behind health states yet to be discovered (Figure 1). Because each individual’s microbiome is unique, it follows that no two persons may process the same foods identically and/or derive the same benefit, ultimately making microbiome analysis a possible ideal embodiment of approaches to precision nutrition. However, based on publicly available human microbiome research, we are far from understanding this complex biomarker and thus it is premature for use as an independent nutrition personalization tool.

**Contributors to microbiome variation**

The term "dysbiosis" is used liberally in the context of microbiome-pathology associations. However, aside from its simplistic definition as a "microbial imbalance", little is known about the functional aspects of what constitutes an imbalance in the gut microbiome at the level of an individual. As essentially all references to dysbiosis stem from taxonomical interpretations, little is available in the way of mechanistic understanding (2). Before we can confidently label an individual's gut microbiota as
in dysbiosis, we need to understand the definition of "eubiosis", yet another ill-defined (and highly individualized) state corresponding to a well-balanced gut ecosystem. Characterizing an individual’s eubiotic state is essential to precision nutrition approaches, particularly among a generally healthy cohort. However, most reports to date have not yet identified a microbiome core within a population, where individual microbiome diversities tend to fit on a continuum rather than clustering into discrete groups (3). Multiple factors contribute to this variation, and while the scope of this perspective is not inclusive of all the possible contributing personal features to the variability in microbiome compositions, we consider those that may play significant roles.

**Host genetics and geographical location**

Individual host genetics contribute a relatively minor portion of the variation within a person's microbiome, with lifestyle factors such as long-term diet substantially outweighing the contribution of any single nucleotide polymorphism (SNP) (4). Xu et al. calculated the heritability of α-diversity to be in a modest range of 3.5 to 10.3%; when they performed a genome-wide association study (GWAS) for enterotypes, no statistically significant signals were found (5). These results reflect a consensus that genetics’ impact on a person's microbiome composition is outweighed by lifestyle, geographical, and/or cultural factors (6). However, this does not mean that host genetic variation is not a factor to consider when analyzing generally healthy individuals’ microbiomes on the species level. For example, borrowing from the literature of microbiome-disease correlations where the data are plentiful, Mendelian Randomization (MR) studies show genetic predispositions to certain conditions such as chronic kidney disease have causal effects on specific bacterial species abundance (5). Such findings demonstrate the potential of leveraging large GWAS datasets such as the UK Biobank toward understanding similar host genome-microbiota dynamics in the generally healthy population. For example, the results of some MR efforts indicate a significant impact of gut microbiome species on health span-related blood phenotypes such as lymphocyte count, eosinophil count, apolipoprotein A1, high density lipoprotein (HDL), total cholesterol, body mass index (BMI), resting heart rate, and blood pressure (7-9). On the other hand, an
established single nucleotide variation in the LCT gene associated with lactase persistence positively correlates with Bifidobacterium abundance, including a large meta-analysis of over 18,000 individuals from diverse populations (10). This particular host-microbiome dynamic appears to be a symbiotic compensatory mechanism to facilitate lactose digestion in those who do not produce sufficiently active lactase enzyme (20). Kurilshikov et al. also reported a persistent SNP-microbiome association between FUT2 (fucosylated mucus glycan secretor/non-secretor) variant and Ruminococcus torques genus group (10). Thus, certain host genetic variations that correlate with the enrichment of particular gut bacterial species can explain host health state phenotypes (such as HDL or BMI) and, conversely, different subsets of SNPs that associate with particular host predispositions (such as lactose intolerance) can impact the composition of the microbiome. Exploration of such dynamics is in its infancy in generally healthy people and, though the effect sizes are likely to be small relative to the aforementioned non-genomic factors, they may ultimately add more granular insight on the level individualized interventions. Such detailed analysis could only be useful once the more salient microbiome influencing factors, such as geographical location, are first accounted for.

After examining hundreds of health status phenotypes in over 7,000 individuals from 14 regions within the Guangdong province of southern China, He et al. found that host location explained the bulk of the microbiota variation (11). Geographical location was found to explain approximately 5- times the variation in the microbiomes relative to the next largest factor, occupation (11). This finding suggests that, in addition to the already challenging task of identifying dysbiosis on the individual level, defining a baseline eubiotic state for an individual would have to account for the region where they live. Thus far, there appears to have been no such effort in the generally healthy populations. However, an approximation of healthy reference ranges within a subset of bacterial taxa yielded confidence intervals that spanned orders of magnitude (12), perhaps in part because no adjustment for geographical location was possible. While likely still relevant when diagnosing clinical conditions, such wide reference ranges may not yet enable precision approaches to lifestyle interventions until adjusted for geographical region and some of the other confounding factors discussed below.
**Effect of medication**

Reports reveal that there is likely a measurable impact of prescription drugs, over-the-counter medications, and dietary supplements on species-level microbiota, yet the effects of most of these products remain unexplored. Vila et al. reported over 150 associations between individual taxa and 17 categories of drugs, with proton pump inhibitors, laxatives, metformin and vitamin D supplements showing the most associations (13). While some medications may impact the microbiota directly, e.g., as demonstrated for metformin (14), others (such as laxatives) may do so by modifying transit time, which has been cited as one of the strongest explanatory factors for microbiome composition (15). The in vivo picture may be quite dynamic as individuals can modify their behavior based on medication intake, e.g., an individual may alter their diet due to nausea or other untoward side effects of the medication or having lower quality of sleep. Thus, precision nutrition approaches to optimize an individual’s microbiome should account for intake of medications and dietary supplements at baseline, as shifts in bacterial species induced by these agents may preclude accurate precision nutrition recommendations if they are based on reference populations following different regimens.

**Long-term diet strongly influences microbiome composition**

As described in several comprehensive reviews, a plethora of evidence suggests that one of the strongest contributors to inter-individual host microbiome variation are long-term dietary habits (16-18). The standard Western diet, low in fiber and high in processed ingredients and saturated fat, has been reported to lead to less diverse gut microbiomes and metabolite outputs that appear detrimental to host health. Dietary-induced microbiota composition shifts such as those resulting from a Western diet intervention can lead to exposure to bacterial components toxic to the host (e.g., endotoxins), and result in gut barrier disruption and metabolic endotoxemia (19). In contrast, certain dietary patterns rich in fiber and polyphenols have been shown to have protective effects against the adverse effects of the standard
Western diet, in part mediated by an increased production of short chain fatty acids (SCFAs) such as butyrate. Some dietary fibers are fermented by bacterial enzymes into SCFAs which, in addition to supplying enterocytes with energy, act as metabolic signaling molecules and histone deacetylase (HDAC) inhibitors, resulting in immune system modulation, as well as influencing transcription and regulation of appetite (17, 18). Additionally, consumption of protein sources rich in L-carnitine and/or choline leads to the production of trimethylamine (TMA) by the microbiome, which, when oxidized to trimethylamine N-oxide in the liver, is associated with an increased risk of cardiovascular disease (17).

**Baseline microbiome features and metabolic capacity**

In the generally healthy population, perhaps the most pertinent application of microbiome analysis is in predicting individual responses to nutritional and lifestyle interventions. If an individual’s baseline metabolic capability is known, it may be possible to tailor dietary fiber recommendations, for example, as the same carbohydrates may not benefit all, depending on their baseline microbiome signatures (20). Reports on the effect of probiotic supplementation on the gut microbiome suggest generally beneficial outcomes, although data also suggest a stratification of responders vs. non-responders to such interventions by baseline microbiome composition and possibly host genetics, as demonstrated with lean donor fecal transplants to individuals with metabolic syndrome (21). Suez et al. further demonstrated that probiotic supplements may delay the re-establishment of a homeostatic gut environment after a course of antibiotics (22). Our understanding of which microbiome signatures correlate with responsiveness to specific foods is rudimentary. Ultimately, deep knowledge of and multi-omics modelling of the metabolic pathways inherent to a particular microbiome signature could allow for tailoring precise dietary interventions that modulate targeted metabolites associated with host health (23). For example, if a TMA-overproducing host microbiome signature is identified, one could minimize sources of carnitine and choline for the individual. On the other hand, another individual may harbor microbes that produce a marked post-prandial glucose (PPG) response to starchy carbohydrates while
minimizing TMA production. In this case, one might be able to recommend a diet higher in animal protein and lower in starchy carbohydrates.

Specific examples are now available of baseline microbiota-driven dynamics; e.g., Korpela et al. reported on particular Firmicutes species, *Eubacterium ruminantium* and *Clostridium felsineum*, that correlate with responder vs. non-responder status (24). These investigators found that while some individuals benefit from a particular dietary intervention, others showed no or even adverse responses, each explained by their baseline microbiomes (24). Similar findings from the Weitzman Institute in Israel have linked gut microbial signatures to post-prandial glucose responses (PPGRs), where microbiome features strongly correlate with blood sugar responses to foods (25). Other results revealed that white bread may be advantageous to some over traditional rye wheat bread based on personalized microbiome signatures (26). This research is beginning to validate the adage that “one man’s cure is another man’s poison”. Nonetheless, replication is warranted of these findings in larger populations in order to enable personalized recommendations in diverse groups.

To validate the microbiome-PPG algorithm described above, Mendes-Soares et al. implemented the same methods reported by Zeevi et al. in 327 free-living American Midwesterners followed for PPGRs to foods (27). While the data were qualitatively replicated, with the microbiome contribution predicting PPRGs at $r = 0.62$, the model underperformed relative to that in the Israeli population, suggesting that further research remains to be done before we can confidently use microbiome biomarker as an accurate predictors of PPGRs across populations (28). In an independent cohort of over 1,000 deeply phenotyped individuals, Asnicar et al. attempted a comprehensive evaluation of the interplay of long-term diet, microbiome composition, and hundreds of fasting and peri-prandial cardiometabolic blood biomarkers (29). They only partially replicated the Israeli cohort findings by Zeevi et al, with overall microbiome features explaining relatively little of the variation of glycemic indexes relative to blood lipids and inflammatory biomarkers (25, 29). The PPGRs showed a marginal association with the gut microbiome (AUC = 0.6), again potentially highlighting the importance of examining different populations toward replicating microbiome-phenotype associations. This task is not trivial as host-
microbe dynamics are complex and results may seem contradictory depending on the details of what parameters are being measured. For example, in addition to demonstrating significant associations of food groups and habitual diet with microbiome features, Asnicar et al. noted differential effects of certain bacterial species of fasting vs. postprandial rises in biomarkers: Flavonifractor plautii was associated increased systemic inflammation biomarkers such as fasting GlycA, but this was decoupled from the biomarker’s postprandial rise, where the same species was correlated with a decrease in GlycA. Several other immunological and some blood lipid biomarkers followed an analogous microbe-blood metabolite dynamic (29). These results highlight the intricate complexity of the microbiome and the need to better understand mechanisms before utilizing an individual’s microbiome composition in the context of precision nutrition.

Certain microbiome features whose association with host health has been relatively consistently replicated in the literature may still not be ready for implementation in precision nutrition platforms. One such example is the commensal Akkermansia muciniphila, a well-characterized gut bacterial species that has shown potential for some clinical utility with regard to obesity (30). In the trial conducted by Asnicar et al. encompassing over 1000 deeply-phenotyped individuals, this beneficial species was not among the main players correlating with cardiometabolic health (29). However, a proof-of-concept clinical trial using both live and pasteurized versions of a A. muciniphila probiotic did show slightly improved insulin sensitivity, reduced insulinemia and total cholesterol, as well as fat mass reduction in individuals with obesity (30). These results demonstrate the potential of microbiome analysis holds for facilitating novel probiotic approaches toward improving cardiometabolic health outcomes. However, they also highlight our distance from being able to rely on an individuals’ gut species abundance metrics for improving health outcomes. This lack of replication of species-level microbiome results will need to be addressed before they can be reliably applied to precision nutrition platforms. This dearth of replication can, in part, be explained by factors that confound microbiome analysis.
Stochastic effects and confounders of microbiome composition analysis

The majority of human microbiome studies fall short of assigning causal effects of the gut microbial environment on host phenotypes (31). Thus, it cannot be discerned whether the gut microbiota composition was affected prior to an intervention or whether the bacterial populations present are a consequence of the intervention itself. This situation is in contrast to studies using rodent models, where investigators often report a transfer of pathological phenotype, but then make often misplaced causal inferences with regards to human hosts (32). Indeed, animal-based microbiome research may have played a role in overstating the causal effects of the microbiota in human health and disease. Moreover, there is a paucity of longitudinal studies tracking shifts in the gut microbial populations toward developing the concept of a core healthy microbiome. David et al. undertook such an exercise in mapping the effects of 10,000 longitudinal human wellness measurements to daily gut and salivary microbiota shifts through a period of one year for two individuals (33). They confirmed that, on the community level, the microbiome was stable on a scale of months but noted that activities such as travel throughout various parts of the world can instill profound changes. In addition to the aforementioned strong influence of geographical location on microbiome composition, multiple reports have indicated that the microbiome does entrain on diurnal rhythms which, if disrupted by interventions such as jet lag or sleep loss, can lead to dysbiosis (34). Caporaso et al. reported a marked variability in two individual’s microbiota at the sequencing depth examined, suggesting that no core microbiome exists at high abundance as only a small subset of the bacterial taxa were found to be consistently present across all samples even day-to-day (35). Others who have examined larger cohorts (though at reduced sampling frequency) have suggested that a single measurement of the unperturbed fecal microbiome can supply long-term insight on composition and metabolic potential (36). The apparently different conclusions drawn by these researchers may be inherent to the respective study designs: fewer subjects enable more frequent sampling and can reveal day-to-day variance, while larger studies are not powered (due to cost) to detect significant longitudinal variances. In practice, the sampling frequency may ultimately be dictated by pragmatism and individual
lifestyle dynamics. Importantly, any approach should ensure that samples are processed using identical procedures leading up to point of data analysis.

As noted, the reproducibility of microbiome associations across independent studies is low, with a significant methodological confounder being the DNA extraction step (10). Other confounding variables include improper and/or inconsistent documentation of sample collection and processing, and yet-to-be standardized data processing and analysis methods (1). It appears clear that stool consistency, described with the Bristol Stool Index (BSI), is often referred to as the single personal factor with the largest effect size on microbiome composition variation in healthy individuals (37). Further, some estimates put the cumulative explanatory power of wellness and lifestyle variables on inter-individual microbiota variation at less than 8% (38). This suggests that much of the variation remains unexplained, with some reports proposing that microbiome-host associations reported to date may be overstated (39). As part of their suggested remedy to this challenge, Vujkovic-Cvijin et al. have offered an essential methodological approach to data analysis that involves case-control matching for confounding variables that strongly associate with microbiome composition (39). They point out that much of the difference in microbiomes between disease cases, such as type II diabetes and irritable bowel syndrome, and controls is diminished once both are matched for alcohol intake or BSI. Approaching independent datasets with consistent analytical rigor can help reduce spurious findings and increase the number of studies which are able to reproduce associations between health status and gut microbiota, thus beginning to make this complex metagenomic biomarker also ripe for more scalable precision nutrition applications in the generally healthy.

**Concluding Remarks**

The determination of individual microbiome composition holds potential to be an important tool for precision nutrition in addition to the currently available personal data derived from blood and various genome, epigenome, metabolome, and emerging glycomic biomarkers of health and healthspan. However, until microbiota associations are more consistently replicated, and randomized clinical trials
and/or other longitudinal cohort approaches revealing causal effects of modifying the microbiome on wellness (not just clinical) phenotypes, the interpretation of individual microbiomes toward personalized recommendations remains a challenge. Importantly, since intra-individual microbiome composition variability has been established as much lower than inter-individual differences, it follows that each individual should harbor personalized species abundance averages that define their state of health. Nonetheless, even within-person microbiome variability may be partly a function of the frequency of sampling. Thus, temporal variability should be adjusted in longitudinal samples toward establishing individualized bacterial abundance metrics that would allow for more accurate assessments of metabolic capacities and facilitate “thresholds” for triggering personalized recommendations. Until microbiome analysis matures to a stage where consistent bacterial species-functional effects have been demonstrated in independent studies spanning various demographics, it appears be premature for metagenomics, in and of itself, to serve as a cost-effective solution or a reliable biomarker of wellness in individuals who are generally healthy. However, casting a wide -omics net, including metagenomics at the individual level, in future longitudinal studies, such as the NIH Nutrition for Precision Health program, should enable n-of-1 study approaches toward realizing microbiome’s full potential in precision nutrition (40).
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Figure 1. Microbiome Composition Analysis in Generally Healthy Individuals. In the generally healthy individual, microbiome composition analysis alone currently offers limited actionable health insight that cannot be readily obtained via more traditional means such as blood chemistry and lipids, activity trackers, and basic biometrics. These validated metrics of physiological and metabolic health allow for optimization via established reference ranges that correlate with healthy states, whereas individual-level optimal microbiome features have yet to be elucidated. Often considered to be a marker of health, high alpha-diversity within the gut microbiome can be qualitatively approximated via traditional measures. However, as this field of research progresses toward the ability to establish optimal microbiome composition baselines at the individual level, metagenomic analysis holds dramatic potential for the practice of precision nutrition.
Acknowledgments:

BN and JB wrote the manuscript. MJ and GB provided insight and commentary on the manuscript.

All authors have read and approved the final submission.