Perspective: Use diet as a tool, not a treatment

Scientists can sequence your microbiome, but they still can't tell you what to eat to prevent or treat disease, says Peter J. Turnbaugh.

A recent report[1] about the health consequences of eating red and processed meat renewed long-standing debates about what evidence should be required before the public are told what foods they should avoid. For me, this subject hits especially close to home — my lab's research shows that meat consumption alters the human and mouse gut microbiomes, and I am frequently asked if meat is "bad for gut microbes".

Our results indicate that meat consumption promotes the growth of bacteria that exacerbate mouse models of inflammatory bowel disease and decreases the levels of bacteria that metabolize fibre[2]. But our studies in both people and mice have been short, controlled and extreme in terms of the level of meat consumption. Does this really reflect what happens in people on more typical diets?

Basing dietary advice on microbiome studies also assumes that it is possible to predict the health effects of different microbial communities — a goal that is far from being realized. Even well-studied mechanisms have unclear consequences for human health. Take, for example, the production of short-chain fatty acids (SCFAs) from the bacterial digestion of fibre. SCFAs act on multiple tissues and targets of interest in both bacterial and host cells. Furthermore, not all SCFAs are the same, and they have not been considered in the context of products of carbohydrate and amino-acid fermentation — let alone the diversity of other microbial metabolites that could enhance or counteract the effects of these specific compounds. Therefore, although it is tempting to recommend diets that boost SCFAs to prevent metabolic and other diseases, the broader effects on the microbiome and its complex interactions with the host are hard to predict.

Another massive gap in our knowledge is the degree to which the microbiome is affected by, or mediates, the health consequences of our diet beyond macronutrients (fats, proteins and carbohydrates). Results from our lab have shown that the effect of raw potatoes on the gut microbiome is markedly different from that of cooked ones[3]. Although cooking-induced changes to carbohydrates explained much of this effect, our data also suggest the broader chemical diversity of plants should be considered. Other research has highlighted the ability of gut bacteria to inactivate potentially harmful chemicals formed during cooking[4]. These results make clear that researchers studying the interaction between diet and the microbiome need to consider not just the composition of foods, but also how they are prepared.

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The research questions pertaining to diet and the gut microbiome are wide open. It is all the more important, therefore, that we identify reliable ways to use the data that emerge as we improve our understanding of how the microbiome works.

Two clear strategies for using microbiome data can be borrowed from more conventional drug development: biomarker discovery and target-driven screening. The use of gut microbes as biomarkers was pioneered by Eran Segal at the Weizmann Institute of Science in Rehovot, Israel, (see page S19) whose group used microbiome profiles alongside other data to predict blood glucose levels following a meal. Although the added value of microbiome data for that particular application remains debated, the general limitation of these approaches is that they provide little information about the mechanisms involved. That makes it difficult to infer causal relationships, to develop mechanistic hypotheses, or to expand these predictors to incorporate future discoveries about the host or microbiome.

The other approach, selecting specific bacterial targets for modulation by diet, has been applied to the design of diets to treat undernourished children[5]. Prototype diets were designed with the goal of promoting the growth of bacteria that are under-represented in children with severe acute malnutrition. Following extensive preclinical characterization of these microbes in mice and pigs, the researchers ran a randomized, double-blind controlled feeding study that provides preliminary support for efficacy in people. This target-driven approach offers a clear advantage over biomarker discovery — it is easy to see how future mechanistic insights into the components of the microbiome with compelling links to disease can be incorporated into the development of therapeutic diets.

As the amount of research into the interactions between diet and the microorganisms that populate our gut grows, it is worth considering whether dietary recommendations are the best way to use our growing knowledge about the role of the microbiome in nutrition. Adjusting the type or quantity of food eaten is an attractive intervention, given its simplicity, but a restrictive diet can be difficult to maintain over long periods of time — especially for people with severe disease. In the future, researchers might instead use diet as a discovery platform in humans and animal models to uncover specific species, genes or enzymes that could be targeted using conventional small molecule drugs, biologics or cell-based therapies. If so, rather than 'what should people eat?' maybe the question should be 'how can we design the microbiome-based medicines of the future?'.

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