Cell

# Microbiome Research in a Social World

**Should we get our microbiomes sequenced? Do we shape our microbes, or do our microbes shape us? These are just a few of the questions at the border between microbiome science and humanities.**

Microbiome research has gone from being a relatively niche corner of microbiology to one of the most-talked-about areas in science in less than 2 decades. However, despite many promising studies, microbiome research has yet to affect most people's daily lives. The microbes themselves, however, are a different story.

"You influence your microbiome every day, whether you choose to or not—by where you live, what you eat, which people you choose to associate with, and so forth. So [if] people take control of that, it could have an enormous impact on their health," says Rob Knight of University of California, San Diego. The question, to Knight and others, is not whether microbiome research will eventually change public health but how.

## Underdog Appeal

The idea of the microbiome—a vast network of neighborly microbes that live in, on, and around us—intrigues many non-scientists. Science journalist Ed Yong, who recently wrote a *New York Times* best-selling book on the microbiome, attributes the concept's appeal to the way it reframes "germs."

"It makes everything that we think we know newly unknown and unfamiliar," Yong says. "As a storyteller, I think that this makes for great stories. Microbes are like underdogs. They were feared and neglected, and now they are starting to get their moment in the spotlight."

At the philosophical level, the microbiome suggests that ecological interconnectedness—with an unseen world of "germs," no less—is part of what it means to be human. "We all think of ourselves as individuals, and we all have this idea of 'self' that's predicated on that," Yong says. "The science of the microbiome subverts that because it shows that every individual is, in fact, this entire community of organisms, only one of which is human."

Microbiome science also sheds light on some long-observed but unexplained correlations. For instance, patients, family members, and healthcare workers have been saying that many neurological conditions go hand-in-hand with gastrointestinal (GI) problems for years. "If you look in the literature or talk to people across many different neurological conditions—Alzheimer's, schizophrenia, depression, and anxiety—the notion that there are GI implications is obvious," says microbiologist Sarkis Mazmanian of Caltech. Until recently, few researchers followed up on these leads. However, research by Mazmanian's group and others has revealed that the gut bacteria have far more influence on human brains than anyone expected.

Microbiome research has even shifted scientists' sense of which biological materials are important. "Whether it's poop or sputum from the lungs, in the past, those would have been considered waste, but now through microbiome research, those are considered highly valuable. And it's not clear exactly whether we ought to regard them as 'human' samples or something else," explains Kieran O'Doherty, a social psychologist from University of Guelph in Canada who studies social and ethical implications of science and technology. "If I give part of my microbiome to researchers, is that something that is still connected to me?"

The answers to those questions could influence microbiome research, O'Doherty says, because ethical and privacy standards for handling human samples tend to be stricter than for handling microbial samples.

## Beware the Hype Bubble

Both microbiome experts and observers are wary of high expectations for the fast-growing field. Yong recalls getting a case of déjà vu while listening to talks at a microbiome-themed conference in 2012. "It sounded exactly like all the hype around the Human Genome Project when the Human Genome Project was still a thing in progress," he says. "You could swap out the word 'human genome' for 'microbiome' and have exactly the same type of claims."

Probiotics are already a multi-billion dollar industry, but there's scant evidence of commercial probiotics achieving what their manufacturers claim they can. While many researchers agree that probiotics could be useful someday, they also agree that there's potential for side effects and that the research "isn't there yet."

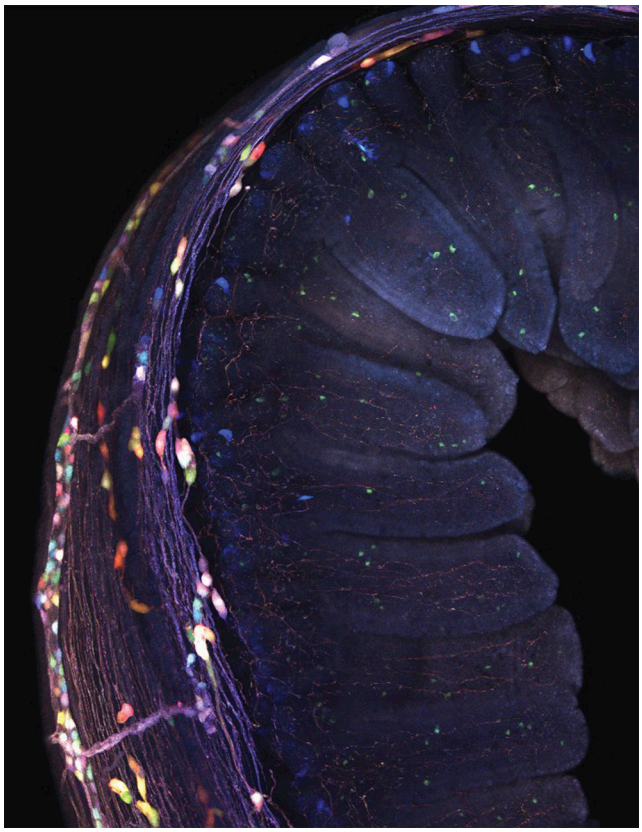
"I think there's a tendency to treat any new, hot area of science as *the* explanation for all these mysteries that have plagued us for a long time," Yong says. "Everyone wants simple explanations, and everyone wants equally simple fixes. And I think the microbiome provides neither of these things." He's quick to add that the microbiome clearly influences many dimensions of human health, but being influential isn't the same as being the font-of-all-cures.

## To Sequence or Not to Sequence

Many microbiome projects, such as Rob Knight's American Gut project, rely on citizen scientists collecting samples of their own fecal microbiome and sending them to labs for sequencing. For most participants, microbiome sequencing is an act of pure curiosity.

Some microbiome initiatives tell participants the species composition of their sample. "We've been very clear about the point that American Gut is not intended as a clinical diagnostic test. It's a Citizen Science project," says Knight. "Just because it's possible to tell the difference between healthy and diseased people in a carefully controlled study, in a rigorously controlled cohort, that doesn't mean you can do it in the general population."

"I don't think anyone can state with a straight face that they can look at your microbiome and make predictions about your health," says Mazmanian. "But that



The gastrointestinal tract is comprised of many different cell types that produce an even more diverse milieu of bioactive molecules. This image is a cross-sectional view of the mouse small intestine with labeling of enteric neurons and their projections. Credit: Bryan Yoo (Mazmanian Lab)

doesn't mean that we won't be able to do that 5 years from now."

Mazmanian argues that if healthy people get their microbiomes sequenced now, it may help them further down the line. Microbiomes vary not just between individuals but also over time. Knowing what a particular person's healthy baseline looks like could be helpful for their future doctors.

Furthermore, sample donations from healthy individuals are essential for the databases that will allow researchers to identify disease signatures in the first place. Rashmi Sinha, a senior investigator at the National Cancer Institute, is leading an effort to build one such database in order to search for microbial signatures that correlate with cancer onset.

"The majority of studies that have been done have been case-control, which means that people already have the disease by the time we look at the microbiomes," Sinha says. "We don't know whether it was the disease that changed the microbiome or whether the microbiome actually caused the disease."

In the search for predictive signatures, amassing a large number of samples is key, Sinha says. Even common cancers only occur in relatively small minorities of the general population. Colorectal cancer, for example, is diagnosed in about 4.3% of US men and women at some point in their lifetime, according to data from the NCI spanning the years 2012–2014. The vast majority of healthy people in a database will never go on to develop the cancer in question. So while there are few immediate benefits to healthy people who are getting their microbiomes sequenced now, doing so may help the public health in the long run.

Downsides to microbiome sequencing include the cost, which many projects pass on to the consumer, and concerns about who will have access to the data in the future.

## There's an App for That?

Even with predictive signatures in hand, getting personalized recommendations to private citizens may be a hurdle. DayTwo, one of the first companies to offer customized microbiome-based health advice, uses an app to reach its customers. The app is grounded in peer-reviewed research on blood glucose responses to food. It uses microbiome data to suggest meals that will keep users' blood sugar at optimal levels.

The basic research behind the DayTwo app is still ongoing. "We are working more and more on trying to ask which features of the microbiome are most predictive," computational biologist Eran Segal of the Weizmann Institute of Technology explains. Figuring out which factors are most relevant to glycemic responses is not only important for scientific understanding but also for creating a tool that non-scientists can easily use.

Gathering dozens of data points takes time, and complicated health apps tend to lose users. At the same time, scientists and app developers are wary of oversimplifying. "The science is complex," says Segal. "One of the biggest challenges is: how do you convey the information that's very multi-dimensional and complex in a way that would be [accessible]?"

## Microbiome Interventions in a Social World

Infrastructure and cultural practices can profoundly shape microbiomes, but those factors fall outside most microbiologists' expertise. Therefore, some researchers advocate for integrating social scientists into microbiome studies.

For example, anthropologist and director of Science and Technology Studies at New York University Amber Benezra spent several years working with microbiome science pioneer Jeff Gordon and his lab at Washington University in St. Louis. When Gordon lab members went to Dhaka, Bangladesh, to investigate links between malnutrition and gut microbiome composition, Benezra was part of the team. While the microbiologists collected fecal samples, Benezra gathered information about the social lives of the study subjects—what they ate, where they cooked, who lived together, and other social data points that could affect microbiomes.

"[We] were thinking about things like access to clean water, poverty, hygiene, sewage, infrastructures—all those sorts of things that are the bigger sorts of things that can affect microbes but aren't necessarily treatable with microbiome interventions," she says.

Understanding how microbiomes fit into existing infrastructure and cultural practices can help microbiome researchers design more effective and culturally compatible solutions to microbe-related problems, Benezra says. Malnutrition is just one example of an issue where collaborations between social scientists and microbiome researchers may be helpful.

The ultimate test for potential interventions will be whether people can adhere to them outside of laboratory environments. "We've seen so many failed interventions, especially in terms of global health because of the missing community involvement or [missing] social [science] thinking," says Benezra. For example, Bangladeshi public health workers encourage citizens to boil water to kill disease-causing bacteria before drinking it. During her fieldwork, Benezra noticed that many people had heard about the campaign but couldn't follow the guidelines because their access to stoves was very limited. The researchers behind the campaign hadn't considered stove access while planning.

## Many Paths Forward

At this stage, it's largely unclear what form microbiome-based therapies will take. Fecal transplants are already saving the lives of people infected with *C. dificile*, but many researchers think that future microbiome-based therapies will be focused on particular bacterial strains or even individual molecules.

For example, Sarkis Mazmanian has spun his academic research into a start-up called Axial Biotherapeutics. The company plans to identify bacterial species, pathways, and molecules that influence cognition and develop them as treatments for neurological conditions like autism and Parkinson's. The company plans to focus on pathways and molecules. "If there were a negative effect, it's much easier to remove a single organism than to reverse a fecal transplant, which I'm not sure is at all possible," Mazmanian says.

However, the microbiome's influence on cognition isn't confined to atypical nervous systems. Studies have indicated that gut microbiome composition shapes physiological responses to chronic stress. Subtle imbalances in otherwise healthy people's microbiomes can contribute to asthma, allergies, and mood disorders amid dozens of other conditions.

"Where I would love to see scientists go one step further [is] to say, 'What was wrong in the environment in the first place that led to the problem?'" says Kieran O'Doherty. For example, some researchers think that high-fat "Western diets" may be contributing to the rise of chronic conditions like irritable bowel syndrome (IBS). Promoting healthy diets could be a very effective way to reshape people's microbiomes for the better, even in people without clinical diagnoses.

Microbiome research has come a long way but still has far to go. Knight likens the current state of the field to the early days of photography. "We're still very much at the stage where you have to build your own dark room and mix your own chemicals," he says. "When you get to the point where you can just record a video on your cell phone and think nothing of it, that opens up all kinds of applications that we can't even imagine now."

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