

A detailed scanning electron micrograph (SEM) showing the surface of human cells, which appear as large, rounded, and textured structures. Scattered across these cells are numerous small, yellow, rod-shaped bacteria. The background is dark, making the cells and bacteria stand out.

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Trillions of microbes call our body home.

THE MICROBIOME MENAGERIE

Now we're learning they're crucial for our health.

BY **ROBIN MARANTZ HENIG**

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A scanning electron micrograph (SEM) showing numerous yellow, rod-shaped Escherichia coli bacteria. The bacteria are densely clustered in several areas, particularly in the upper left and center, and more sparsely distributed in others. They are situated on a highly textured, purple, and irregular substrate that resembles biological tissue or a complex surface. The lighting creates strong highlights and shadows, emphasizing the three-dimensional nature of both the bacteria and the surface they inhabit.

Escherichia coli, the yellow rods clustered on a purple substrate, can cause food poisoning, but most strains are not only harmless, they're beneficial. *E. coli* inhabit the human gut and perform essential functions, such as making vitamins K and B₁₂ and repelling disease-causing bacteria.

FECES

The gut microbiome flaunts its diversity in this sample of human feces, which includes an enormous bacterium that's about 50 times longer than *E. coli*. Everyone's mix of microbes is unique. Scientists are learning the many ways these microbes affect our health, weight, mood, and even personalities.





THE MORE SCIENTISTS investigate the microbes living inside us, the more they learn about the surprising impact of these tiny organisms on how we look, act, think, and feel. Are our health and well-being really driven by the bacteria, viruses, fungi, and protozoa that live in our intestines, in our lungs, on our skin, on our eyeballs? What a weird concept—that the bugs we lug around appear to be essential to establishing the basic nature of who we are.

The effects of the microbiome, this menagerie of microorganisms, can be profound—and can start incredibly early. In a study published last year, scientists showed that something supposedly as innate as a child's temperament might be related to whether the bacteria in an infant's gut are predominantly from one genus: the more *Bifidobacterium* bugs, the sunnier the baby.

This observation, from Anna-Katariina Aatsinki and her colleagues at the University of Turku in Finland, is based on an analysis of stool samples from 301 babies. Those with the highest proportion of *Bifidobacterium* organisms at two months were more likely at six months to exhibit a trait the researchers called “positive emotionality.”

Microbiome science is still relatively young. It's been just 15 years since the research took off in earnest, which means most studies to date have been preliminary and small, involving only a dozen or so mice or humans. Scientists have found associations between the microbiome and disease, but can't yet draw clear cause-and-effect conclusions about our vast critter inventory and what it all means for us as hosts. Still, the inventory itself is mind-boggling—it's now thought to be around 38 trillion microbes for a typical young adult male, slightly more than the number of actual human cells. And the prospects for putting that inventory to use are tantalizing.

In the not-too-distant future, according to the most enthusiastic researchers, it might be routine to deliver a dose of healthy microbes in the form of prebiotics (compounds that act as a substrate on which beneficial microbes can grow), probiotics (the beneficial microbes themselves), or fecal transplants (microbe-rich feces from healthy donors)—helping us realize the promise of operating at top form, from the inside out.

When we talk about the microbiome, we're talking primarily about the digestive tract, home to more than 90 percent of a

STREP

Streptococcus pneumoniae, shown dividing into daughter cells, can cause serious illnesses, such as meningitis and pneumonia, but like *E. coli*, some *Streptococcus* species are harmless. The bacteria are found on the skin and in the mouth, respiratory tract, and gut.

Behind the Images

Martin Oeggerli made these images with a scanning electron microscope. The samples were dried, coated with gold, and placed in a vacuum chamber. The microscope's electron beam has a shorter wavelength than visible light and can capture smaller objects, but without color. When the color of a microbe is known, Oeggerli uses it. If not, he chooses colors to discriminate between types of microbes and their features.





LIPS

Moist lips are rich in microbes. A woman pressed her mouth on a petri dish to let her microbiome grow, and grow it did. Days later a colony bloomed. People who often kiss each other will develop similarities in their oral microbiomes.

body's microorganisms. But other regions are also crawling with life. Microbes colonize wherever the inside of the body meets the outside: eyes, ears, nose, mouth, vagina, anus, urinary tract. There are also microbes on every inch of skin, with high concentrations in the armpits, the groin, between the toes, and in the belly button.

And here's the really amazing thing: Every one of us has a particular mix of microbes that's different from everyone else's. Based on current observations, it's possible for two individuals to have zero overlap in the microbial species of their microbiomes, says Rob Knight of the Center for Microbiome Innovation at the University of California, San Diego. The unique nature of microbiomes might even have forensic applications, he says. "We can track objects or surfaces people touch back to that person by matching the skin microbiome traces." Maybe someday police investigators will go through crime scenes taking samples of skin microbes, much the way they now dust for fingerprints.

Here are some highlights of what scientists are learning about how the microbiome affects us across our life span, from infancy to old age.

INFANCY

THE FETUS IN UTERO lives essentially microbe free. Then it squeezes down the birth canal, where it confronts a riot of bacteria. During a vaginal delivery, the baby is awash in microbes that live in the vagina; it's also exposed to the mother's gut bacteria as its face passes by her perineum and anus. These maternal gut microbes immediately start to colonize the newborn's own gut, engaging in a kind of conversation with developing immune cells. In this way, the very early microbiome prepares the immune system for healthy functioning later in life.

When a baby is born by cesarean section, though, it misses out on this exposure. Its gut is seeded with different microbes—not those from the mother's gut and vagina, but from her skin and breast milk, the nurse's hands, even the hospital bedding. These early differences might have implications that last a lifetime.

In 2018 Paul Wilmes of the Luxembourg Centre for Systems Biomedicine at the University

of Luxembourg published a study of 13 babies born vaginally and 18 by C-section. He and his colleagues analyzed the microbes in the stool of the newborns and their mothers, as well as vaginal swabs from the mothers. C-section babies had significantly lower levels of bacteria that make lipopolysaccharides, which are a primary stimulus of the developing immune system. The reduction lasted for at least five days after birth—enough, Wilmes believes, to have long-term consequences for immunity.

Eventually, usually by the first birthday, the microbiomes of C-section babies and vaginally born babies are pretty much the same. But Wilmes thinks the differences he observed in the first few days of life mean C-section babies might be missing a period of "priming," when immune cells are set up to respond appropriately to foreign agents. The scantier microbial populations of C-section babies during these initial days could explain why they are more prone to a host of immune system problems later on, including allergies, inflammatory diseases, and obesity.

Wilmes says one day it might be possible for babies born by C-section to be given probiotics derived from specific strains of bacteria found in their mothers, which would, in theory, seed their intestines with helpful microbes. Such probiotic therapy is still far in the future, though.

CHILDHOOD

FOOD ALLERGIES HAVE BECOME so widespread that many schools restrict what lunches kids can bring from home, like peanut butter and jelly sandwiches, for fear of setting off a classmate's allergic reaction. In the United States, 5.6 million children suffer from food allergies—which translates to two or three in every classroom.

Many factors are thought to account for this rise, including an increase in C-section births and an overuse of antibiotics, which can wipe out protective bacteria. Cathryn Nagler and her colleagues at the University of Chicago wondered whether the rise in childhood food allergies might be linked to the microbial mix in children's guts. Last year they published a study of eight six-month-old babies, half of whom were allergic to cow's milk, half of whom

were not. The microbiomes of the groups were quite different, they discovered: The healthy babies had the bacteria expected in typically developing babies their age, while the babies with a cow's milk allergy had bacteria more characteristic of adults.

In the allergic babies, the normally slow progression from an infant microbiome to an adult one took place "at warp speed," Nagler says.

Using fecal samples, Nagler and her colleagues transplanted gut bacteria from the babies in her study into germ-free mice—mice born by C-section and raised in sterile conditions so they had no microbes at all. When the mice received transplants from healthy babies, they received protective bacteria that prevented an allergic response to cow's milk. But when the transplants were from allergic babies, the mice didn't get the protective bacteria and had an allergic response.

Further analysis showed that one species of bacteria in particular that's unique to human infants—*Anaerostipes caccae*, from the Clostridia class—seems to have been most relevant in protecting the first group of mice. This species was from the same family within Clostridia that Nagler's team had identified in an earlier study as protective against peanut allergy.

Nagler, who is president and co-founder of the Chicago-based drug start-up ClostraBio, hopes to test the therapeutic potential of these bacteria in lab mice—and eventually in allergic patients. The first challenge has been finding somewhere in the gut for the beneficial bacteria to land. Even in an unhealthy microbiome, Nagler says, all the niches are already filled; for Clostridia to go in, something else has to come out. So ClostraBio developed a drug that clears out a niche in the microbiome.

Nagler and her colleagues have been giving the drug to mice and then infusing them with a variety of Clostridia bugs, along with dietary fiber that encourages their growth. She hopes to begin clinical testing on a Clostridia treatment in humans within the next two years, with the eventual goal of giving it to children with food allergies.

Gut microbes also might be related to other childhood diseases, such as type 1 diabetes. In Australia scientists collected stool samples from 93 children with a family history of type 1 diabetes and found that those who went on to develop the disease had higher levels of enterovirus A in their

stool than those who didn't develop diabetes.

One of the scientists involved in the study, W. Ian Lipkin of the Columbia University Mailman School of Public Health, cautions researchers against rushing to explain diseases—whether diabetes or any other—by differences in the microbiome alone. "This is still largely a descriptive science," he says; all that's known for sure is that certain microbes are associated with certain conditions.

Even with this caveat, Lipkin is excited about where microbiome science might lead. He expects that in five or 10 years, scientists will understand the mechanisms of how the microbiome affects the body and will have begun clinical trials on human subjects to demonstrate the health impact of altering it. Once microbiome science "becomes mechanistic and testable," he says, "then it will become real."

ADOLESCENCE

THE VAST MAJORITY OF TEENAGERS in developed countries are pimple-prone—and for them, there does seem to be such a thing as an "acne microbiome." Many kids have skin that's especially hospitable to two strains of *Cutibacterium acnes* (until recently called *Propionibacterium acnes*) that have been closely linked to acne. Most strains of this bacterium, despite the *acnes* in its name, are either harmless or helpful, keeping pathogenic microbes at bay; in fact, *C. acnes* is the predominant component of the normal microbiome of the face and neck.

But having a bad-guy strain of *C. acnes* can be a problem. It's one of the elements needed for acne to arise, says Amanda Nelson, a dermatologic researcher at Penn State University College of Medicine. The others are sebum (the oil produced by sebaceous glands to keep the skin moist), which *C. acnes* uses as a food source; plugged-up hair follicles; and an inflammatory response. These four factors work in concert, Nelson says, adding, "We actually don't know what happens first."

The acne microbiome was the focus of a study at Washington University School of Medicine in St. Louis, where researchers found that the only acne treatment leading to long-term remission—isotretinoin, sold as Accutane and other

SMELLY FEET

Cultured from damp feet, these bacteria, attached here to a fiber, thrive in sweat, which is odorless. But when sweat collects, it creates a breeding ground for odoriferous microbes. More sweat glands are concentrated on our palms and on the soles of our feet than anywhere else.

NEXT IMAGE

BELLY BUTTON

A half dozen types of microbes predominate in the navel. But many other species of bacteria and fungi are also found there. Like the microbiome inside, the microbes outside vary from person to person.





THE MICROBES WITHIN

Approximate number*

38 trillion
LARGE
INTESTINE



1 trillion
DENTAL
PLAQUE



GUT INSTINCTS

Our bodies host trillions of microbes, a collection of bacteria, fungi, and protozoa that starts developing at birth and is unique to each of us. These microorganisms can communicate with our brains to regulate bodily functions and even influence our mood, as well as chronic conditions such as anxiety, through chemical communication pathways known as the gut-brain axis.

HOW THEY COMMUNICATE

VIA BLOODSTREAM AND NERVES

Chemicals released by microbes into nerves or the bloodstream influence brain areas that deal with memory. Chemicals in the bloodstream can also signal the limbic system—a brain area that processes emotion and stress—to change our moods.

THROUGH THE VAGUS NERVE

Sensory neurons receive chemical signals from gut microbes and relay them up this primary signaling path between gut and brain. The brain sends back signals that modify function, such as tempering an inflammatory response so the gut will keep working even if a person is sick.

USING THE 'SECOND BRAIN'

Microbes can bypass communicating with the brain and directly signal the enteric nervous system—a meshlike network of neurons in the digestive tract, sometimes called the second brain—to independently influence gut movements and secretions.

The **vagus nerve** supports pathways of the parasympathetic nervous system, which helps to promote a state of equilibrium in the body.

The biggest community of microbes, more than 90 percent of the body's total, thrives in our **large intestine**.

Enteric nervous system

AREA ENLARGED

*BASED ON A TYPICAL MALE, 20-30 YEARS OLD AND WEIGHING 154 POUNDS

MONICA SERRANO, NGM STAFF; MESA SCHUMACHER, ART BY INTERVOKE. SOURCES: EMERAN A. MAYER, UCLA DIVISION OF DIGESTIVE DISEASES; STEPHEN COLLINS, MCMASTER UNIVERSITY

180 billion
SKIN



100 billion
SALIVA



40 billion
SMALL
INTESTINE



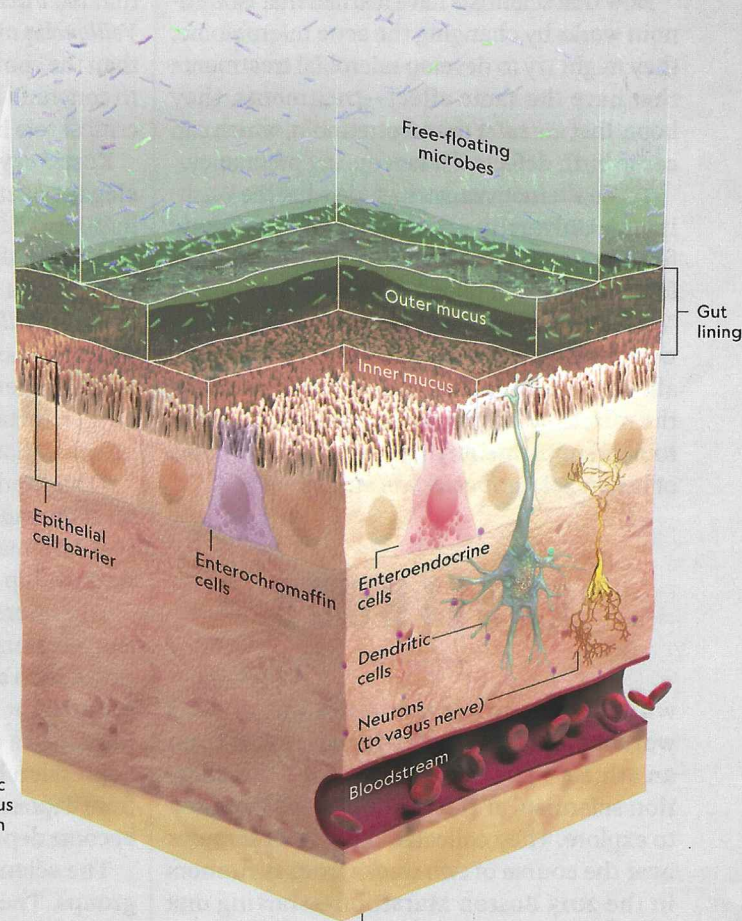
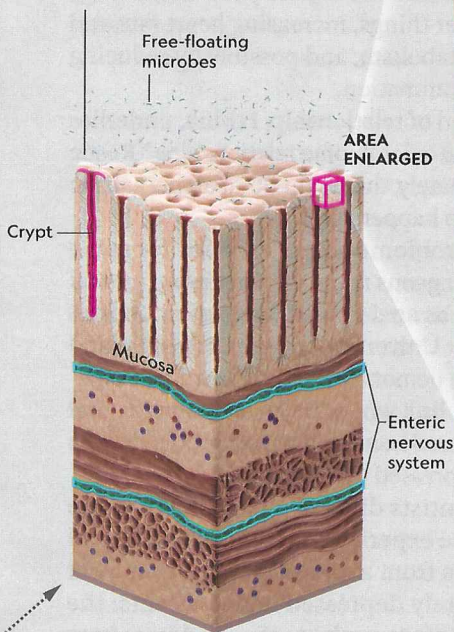
9 million
STOMACH



FRIENDS AND FOES

Microbes in mucosa can work with us. But those floating free inside the intestine tend to focus more on their own survival, sometimes to our detriment, especially if they're harmful parasites.

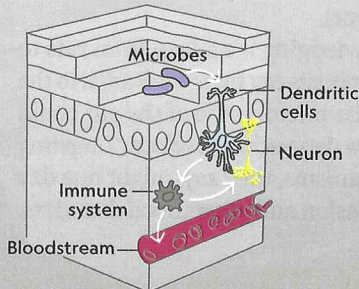
Intestinal depressions called crypts provide a large surface area to absorb fluids and interact with microbes.



WHAT MICROBES CAN TELL US

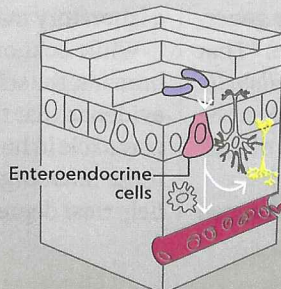
WE NEED AN IMMUNE BOOST

Microbial disturbance in the gut lining can be sensed by immune messaging (aka dendritic) cells. They can then activate other immune cells or signal distress to the brain.



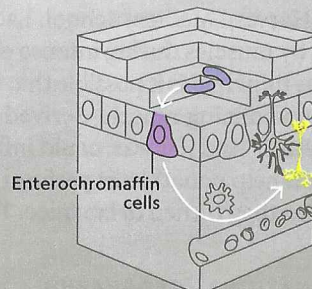
PUT DOWN THE FORK

Scientists suspect that microbes get enteroendocrine cells to release chemicals signaling the hypothalamus—the brain area that keeps our body in balance—to tell us we're full.



WE'RE HURT, OR HAPPY

Microbes can trigger enterochromaffin cells, which hold most of the body's "happy chemical," serotonin, to signal the brain, influencing perceptions of pain and well-being.



brand names—works in part by altering the skin microbiome, reducing the number of *C. acnes* bacteria while increasing the diversity of the skin microbiome overall. In this healthier, more diverse environment, they found, it's harder for the bad strains of *C. acnes* to take hold.

Now that scientists have learned that isotretinoin works by changing the acne microbiome, they might try to develop microbial treatments that have the same effect—treatments, they hope, that are safer than isotretinoin, which can cause birth defects if taken during pregnancy.

These alternatives can include what the Washington University researchers call “prebiotic fertilizers”—microbes that provide conditions for a healthy skin microbiome to flourish—and “strain-selective ‘weed killers’”—agents that wipe out the deleterious strains of *C. acnes* while allowing the beneficial ones to remain. Also in the mix, they say, might be probiotics, oral or topical supplements that contain direct doses of beneficial *Cutibacterium* strains.

ADULTHOOD

WHAT IF YOU COULD GET MORE out of your workout just by transferring microbes from an athlete's gut into yours? That's the question scientists at Harvard University wanted to explore. They collected daily stool samples over the course of two weeks from 15 runners in the 2015 Boston Marathon—starting one week before the race, ending one week after—and compared them with daily stool samples taken for two weeks from a control group of 10 non-runners. A few days after the marathon, the scientists found, the runners had significantly more *Veillonella atypica* bacteria in their stool than did the non-runners.

“It set up a bit of a light bulb because of the unique metabolism of *Veillonella*, which uses lactate as its preferred source of energy,” says Aleksandar Kostic, of the Joslin Diabetes Center and Harvard Medical School. Lactate is generated by muscles during intense exercise. “That got us thinking: Is it possible that the *Veillonella* is metabolizing muscle-derived lactate in the athletes?” And if it was, could infusions of *Veillonella* help nonathletes perform better?

Next they turned to lab mice. They extracted

Veillonella from one runner's stool and infused the bacterium into 16 mice with normal microbiomes that had been screened for pathogens. Then they put the mice on tiny treadmills and had them run to exhaustion. They did the same with 16 control mice, using a different bacterium that isn't involved in lactate metabolism. The *Veillonella* mice could run for 13 percent longer than the control mice, leading the investigators to conclude that the microbiome might play a critical role in physical performance.

Kostic says the experiment offers “a really elegant example of how symbiosis comes to happen.” The *Veillonella* benefits when the muscles of the host, through exercise, generate the lactate it lives on. The host, in turn, benefits because *Veillonella* turns lactate into propionate, which enhances the capacity for exercise by, among other things, increasing heart rate and oxygen metabolism, and possibly by reducing muscle inflammation.

“This kind of relationship, I think, underlies most human-microbiome relationships,” Kostic says. “Ultimately, there's this kind of mutualistic relationship happening.”

The microbiome might account for some less advantageous traits too, including mental states such as anxiety and depression. In 2016 scientists at University College Cork in Ireland published a demonstration of the microbiome-depression link when they transplanted stool from depressed humans into rats. Would the rats become depressed too?

The scientists divided 28 lab rats into two groups. The experimental rats received fecal transplants from a pooled preparation from three severely depressed male patients; the control rats got transplants of pooled feces from three healthy males.

It turned out that getting fecal transplants from the depressed men made the rats depressed. Compared with the controls, they exhibited a loss of interest in pleasurable activities (as measured in rats by how often they chose to drink sugar water), and increased anxiety (which in rats means avoiding open or unfamiliar sections of a laboratory maze).

While acknowledging it's a leap from rats to humans, the scientists say their work adds to the evidence that the microbiome of the gut could play a role in how depression develops. Targeting these microorganisms, they say, might one day help treat depression and other mood disorders.

OLD AGE

THE MICROBIOME IS AT ONCE PERSISTENT and ever changing. Your unique microbiome profile is pretty much set by age four, and only significant changes—altering diet or exercise routines, moving to a different place, changing the time spent outdoors, taking antibiotics or certain other drugs—can really change it. But in one sense, the microbiome is constantly in flux, varying in tiny ways with every meal. And throughout adulthood it changes along a predictable course—so predictable, in fact, that it's possible to estimate your age just by looking at your gut microbes.

This handy trick, known as a “microbiome aging clock,” involves artificial intelligence, as demonstrated recently at the Hong Kong-based start-up Insilico Medicine. The scientists gathered information on the microbiomes of 1,165 people in Europe, Asia, and North America from publicly available data sets. Roughly one-third of the samples were from people in their 20s and 30s, one-third from people in their 40s and 50s, and one-third from people ages 60 to 90. The scientists put the age-tagged microbiomes of 90 percent of the subjects through a round of machine learning; then they applied the patterns found by AI to the other 10 percent of the microbiomes, untagged, to see if they could determine the ages. The microbiome aging clock came up with a suggestion that was accurate to within four years of the actual age.

What does this say about the physical changes that occur with age, in particular weakened immunity, systemic inflammation, and frailty? Researchers at Babraham Institute in Cambridge, England, tried to find out using fecal transplants. They knew the immune system functions more poorly with age, and they wondered whether transplanting feces from young mice into old mice would have a restorative effect.

Before the transplant, the old mice showed a significant decline in the immune reaction of cell masses lining the small intestine known as Peyer's patches. When the old mice were given fecal transplants from young mice, the immune response of their Peyer's patch cells reverted to a more youthful state. Apparently, the scientists concluded, the sluggish immune reaction in old mice is reversible; it can be “rescued”

by an infusion of gut microbes from young mice. It's enough to make you wonder whether a dose of youthful poop could be the secret to a healthier old age.

FECAL TRANSPLANTATION is a hallmark of microbiome research in animals. It's also one of the main clinical interventions being studied for people as a way to introduce microbes that could fight a wide range of diseases.

This is not mere speculation; fecal transplantation has been used for the past decade or so to treat recurrent infections of drug-resistant *Clostridium difficile*, a severe, potentially fatal intestinal infection. About 12,000 to 15,000 medically supervised fecal transplants are done each year in the U.S. alone, according to Colleen Kelly of Brown University, co-chair of the Fecal Microbiota Transplantation National Registry. Generally the results are good, but last June the FDA reported the death of one patient from an infection after a transplant performed with feces that had not been adequately screened for drug-resistant bacteria.

Besides fecal transplants, scientists are studying other methods of manipulating our microbiome, including prebiotics, probiotics, and changes in diet or exercise that might alter the mix of microbes in the gut. But even the biggest boosters of microbiomics say it's hard to draw conclusions yet about the connection between the microbiome and human health, and they urge caution about rushing into therapies.

“There's a lot of excitement around fecal transplantation and the development of the microbiota as drugs,” says the University of Luxembourg's Wilmes, noting that companies are working on new probiotics to “restore an imbalanced microbiome to one that would be in equilibrium to the host.” Which is all very well—as an ecologist himself, Wilmes knows the value of “restoration ecology” in the environment—but it's a bit premature.

“Before we are able to really properly and rationally do this,” he says, “we need to understand what really constitutes a healthy microbiome and what are the functions that the microbiota confer to the human host. I don't think we're there yet.” □

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