World view

By Ruth Ley

The human microbiome: there is much left to do

It's time to make the survey of humanity's 'second genome' more complete.

This week marks the tenth anniversary of the first big survey of microbial diversity in the human body, published in *Nature* by the Human Microbiome Project (HMP) Consortium, of which I was a member.

Before then, microbiologists knew that the body played host to a large mass of microorganisms — a heady mix of bacteria, along with archaea, fungi and viruses, spread over the skin, in the mouth and in the gut — together dubbed the microbiome. But until 2012, we lacked an inventory of them.

In fact, this inventory — an index of 10 trillion cells belonging to thousands of species, weighing a combined 200 grams in each person — is still incomplete. It's time to build on this early work (Human Microbiome Project Consortium *Nature* **486**, 207–214; 2012), and revamp the project to represent humanity in all its complexity.

It took a long time to begin that early work, and the pace of change over the past ten years has been stunning. Only once high-throughput gene-sequencing technologies — first developed to investigate the human genome — became cheap and easy enough to use could the HMP begin.

After launching in 2007, the consortium sequenced the DNA of microbes found in and on 242 people from 2 US cities — St Louis, Missouri, and Houston, Texas, chosen for their proximity to the two pre-eminent sequencing centres of the time, the McDonnell Genome Institute at the Washington University School of Medicine in St Louis, and Baylor College of Medicine in Houston. Our activities were funded by the US National Institutes of Health's Common Fund, and the project pulled in academic microbiome bioinformaticians to work on the data after we'd generated them.

The result was the first comprehensive catalogue of a healthy US human microbiome: a full list of the genes in the microbes in the gut. The HMP showed that the gut's cellular organisms consist of thousands of species, with a genetic footprint 150 times the size of the human genome. Eventually, this abundance led biologists to view the microbiome as an environmentally acquired 'second genome', hidden in the human host.

Ten years on, we know a whole lot more. The microbiome is essential for the proper functioning of our bodies, key to digesting food and staving off pathogens. Experiments in mice have shown that microbiome compositions affect levels of social engagement and anxiety. Common illnesses such as cardiovascular disease and obesity are linked to distinct microbiomes. How babies acquire their microbiomes — and what influences the microbiomes' development — is also becoming clearer.

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(Given how fundamental microbes are to our health, I still find it astonishing that we outsource so many functions to myriad organisms that we pick up from our environment, starting at birth.)

We have plenty of unanswered academic questions, too. Where did the microbiome first come from in human evolution? How are humanity's microbiomes different from those of other primates, mammals or animals more generally? How do microbiomes move from person to person? And what do changing diets and sanitized lifestyles mean for the long-term health of the microbiome?

That first analysis ten years ago, recruiting people from just two US cities, miserably failed to capture the true diversity of the human microbiome. We now know that people living in Europe and in North America have less diverse microbiomes than people living in less industrialized regions — but too little is known about differences across groups of humans.

And even less is known about the multitude of other animals that themselves contain multitudes. We know that the microbiomes of captive animals are different from those of animals living in the wild, in much the same ways that industrialized human microbiomes differ from non-industrialized ones. But most of what we know about animal microbes comes from captive-animal studies. As we lose animal diversity to rapid global change, we're also losing microbiome diversity.

Learning more will require a new consortium, sampling thousands of people and animals. We need wildlife biologists and microbiome scientists working side by side, with crews around the world. Ten years ago, analysis was so new and difficult that we spared little thought for sample acquisition. Now, sample acquisition from sources globally should lead the process.

Some might ask why we need a new, grand, expensive consortium when data are already trickling in — one study at a time, conducted by laboratories working alone. But industrialization moves fast, and modern economic forces have the power to annihilate microbial diversity faster than it can be observed.

A new consortium would empower scientists to finally fill in the microbiome map. It's like a human census: you don't wait for individual towns to report their population numbers; you make a single concerted effort to do it consistently and quickly, before it changes.

A vast new diversity analysis of humanity's microbiome, and of the broader vertebrate microbiome, will finally place our own species' data in the context of the tree of life. Only then can we truly extend the label 'human' to the microbiome.

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Clarification

This World View erroneously stated that some of the participants were from Boston, Massachusetts, owing to their proximity to the Broad Institute. In fact, they came from St Louis, Missouri, which is close to the McDonnell Genome Institute at the Washington University School of Medicine.

Corrected online 11 July 2022