White House announces microbiome initiative but science on gut bacteria still unsettled

When I used to teach microbiology, I would always begin by telling my students that *it's a bacteria's world and we are just living in it.*

I would also often refer to the single-celled organisms as "our bacterial overlords." We may think of ourselves as just human, but we're really a mass of microorganisms housed in a human shell. Every person alive is host to about 100 trillion bacterial cells. They outnumber human cells 10 to one and account for 99.9 percent of the unique genes in the body. The human-centric mindset of my students rejected this lesson but that didn't make it any less true.

Bacteria truly dominate this planet in ways we humans could never even begin to dream of. From the most extreme conditions to the lining of the GI tracts of animals, bacteria colonize close to every nook and cranny of this planet. But they are not stagnant inhabitants either — they also preform some of the most vital functions on out planet. They provide Earth's atmosphere with an abundance of oxygen and the soil with an abundance of nitrogen to allow plants to grow. They also help many animals with digestion and aid in the production of many nutrients and vitamins. They help protect us from pathogens and have recently shown us how to edit genomes with an amazing accuracy.

Despite their importance to our lives, we have not always given these *bugs* their due attention until recently. Interest in the ecosystems these bacteria influence — called microbiomes — has exploded in just the passed few years and we are finally giving these vital organisms the recognition they deserve. In particular the Obama administration has made several decisions that speak to their desire to have microbiomes at the forefront of science policy.

In 2013 President Obama named Jo Handelsman the new Associate Director for Science at the White House Office of Science and Technology Policy. Handelsman is a microbiologist by trade and even served as the president of the American Society for Microbiology. After working closely with scientists and other experts, the culmination of this appointment was a report on the coordinated efforts that are needed to advance the field of microbiology and our understanding of the various microbiomes. The report, titled the Unified Microbiome Initiative (UMI), emphasizes both the need for advances in instrumentation and technology for the field, as well as a placing an importance on better interdisciplinary communication.

The UMI sets lofty goals and projects results in just for a few short years for the many fields influenced by a microbiome, such as human medicine, agriculture, and climate change. While the report does contain some commendable components, the authors fail to place correct emphasis on a few key aspects of microbiome research, which will undoubtedly hold the field back.

Age-old story of correlation vs. causation

Despite what you may see in the media, almost all of microbiome research struggles move from *correlation* — these two events happened at the same time — into the realm of *causation* — one of these caused the other. This is nowhere more obvious than in research links the behavior of the microbiome with human disease. These studies are often unable to determine if a change in the microbiome has

caused the disease or if the disease caused the change in the microbiome.

To their credit the authors of the UMI do not shy away from this fact, writing: “Over the near term of five years, these tools could reorient the field from correlative studies to hypothesis-driven approaches capable of establishing precise causal relationships.” But to move out of this arena will take more than just better technology focused at these microbes, the technology will need to be focused on humans too.

Scientists are quite sure that genetics influence a person’s microbiome. Genes play a part in deciding what bacteria can and can’t grow in and on a person. How and to what extent, is still unknown, but many of the genes that have been identified as having a role in shaping a person’s microbiome are those genes implicated in immunity. This makes sense as the immune system and the microbiome have a very important interplay. Unfortunately, the genome’s role in determining the microbiome’s constituents only serves to complicate the matter.

Take asthma, which has long been believed to have a strong genetic basis, with more than 50 genes implicated in the etiology of this condition. Most of these genes are also involved in immune function. On the other hand, many now believe that asthma is tied to an ‘unhealthy’ microbiome. A recent, popular study from *Science Translational Medicine* claimed to have found that a reduction, or absence, of four genera of bacteria— *Lachnospira*, *Veillonella*, *Faecalibacterium* and *Rothia* — was responsible in some way for the development of asthma.

But taking a larger view of the disease, and incorporating what is known about the microbiome, genetics, and asthma, it’s hard to figure out where to put the horse and where to put the cart.

Are the genes solely responsible for asthma? Do the genes that cause asthma also independently cause the immune system to target these four genera. Are the genes the bystanders in all of this or do the genes only affect the microbiome and then the absence of those bacteria directly cause the disease? Are there environmental factors that vindicate both the microbiome and genetics in this disease?

Asthma and similar diseases that are associated with an “unhealthy” microbiomes are multifaceted and will not be fully understood by focusing exclusively on the microbiome. To effectively elucidate what is causing these diseases, these fancy new instruments the UMI calls for should not only be aimed at our resident microbes, but ourselves and our genes too.

Report lacks culture

The authors of the UMI call for a laundry list of “-omics” to be the focus of microbiome research for the future: genomics, proteomics, metabolomics, transcriptomics, et al. and for this the reported should be lauded. Only a holistic approach to investigating microbiomes will allow us to learn anything from these bugs, but some approaches will yield more translatable and useable results than others and thus research should be skewed in those directions.

One of the best lessons we have learned from studying the microbiome is that context is the most important variable. *Escherichia coli* in the colon producing vitamin K is beneficial, but that same *E. coli* in the urinary tract is a UTI. However, when scientists focus just on genomics and metagenomics too much context is lost.

Studies that focus solely on metagenomics — a technique for identifying many species of bacteria in a sample based on the presence of a single genetic marker — in particular have already cost a great deal of confusion. The most prominent example was in February when researchers, in a now much maligned study, used the technique on the NYC subway and found markers for the causative agents for the plague and anthrax —as well as DNA from two non-native New York insects.

By focusing too much on the who in the story, these metagenomic based studies often leave out the context of the equation. This puts the onus on researchers, journalists, or activists, to fill in the blanks of the story. This is how we can go from “these 4 genera are missing in the microbiome of a few people” to “if we make a probiotic with these 4 bacteria we can cure asthma”.

The point is that everyone is getting far too caught up in *who* found in each study. But historically, the greatest discoveries in microbiology—the ones with the most value to society—have been those characterized by describing *what* the microbes are doing.

It didn’t matter that it was *Thermus aquaticus* in hot springs, what mattered was its heat stable polymerase. It didn’t matter that it was *Penicillium notatum* on Alexander Fleming’s petri dishes, but the substance the fungus was secreting.

So instead of metagenomic or even genomic approaches, microbiome research should focus on the biochemistry of these organisms. To date, the best way to study this has been through the use of agar and broth cultures, a system that has not changed much in the past hundred years. As a result about 99 percent of bacteria remain unculturable, which makes their collective proteomics and metabolomics difficult to study.

We need to focus on advancing ways to culture the 99 percent so we can study the way these microbes live and interact with their ever changing environment. By doing so we may find microbial enzymes that help reduce industrial or agricultural carbon emissions, or proteins that help crops grow faster and with higher yields. We will undoubtedly find more antimicrobials.

The UMI sets very lofty goals over a very short period of time, however, this is necessary to move the field out of the realm of correlation and into biological causation. Changing the focus from the who to the what is vital to realizing the goals of this initiative.

Nicholas Staropoli is a research associate for the American Council on Science and Health. He has an M.A. in biology from DePaul University and a B.S. in biomedical sciences from Marist College. Follow him on twitter @NickfrmBoston.