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Microbiome-Based Diagnostics for Disease: Where Are We Now and Where Are We Headed?

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Guests: Drs. Drew Schwartz and Aayushi Uberoi from the Washington University School of Medicine in St. Louis, Missouri.

Bob Barrett: This is a podcast from *Clinical Chemistry*, a production of the Association for Diagnostics & Laboratory Medicine. I'm Bob Barrett.

In recent years, the term "microbiome" has been popping up more and more frequently as studies have demonstrated the importance of microbial communities in many areas of human health. As the microbiome has gained greater visibility in the public sphere, new opportunities and challenges have presented themselves. On the plus side, increased attention and interest have provided more funding opportunities and interdisciplinary collaborations contributing to forward progress. At the same time, misunderstandings and oversimplification in popular media have led to unrealistic expectations of what microbiome science can and cannot achieve. What microbiome-based diagnostics currently exist, and how are they being applied to answer clinical questions? Can the field advance from the current state to a future that meets the expectations of a demanding public? A Q&A article appearing in the June 2024 issue of *Clinical Chemistry* summarizes the current state of microbiome-based diagnostics and predicts what's next for this rapidly evolving field.

In this podcast, we're excited to speak with two of the article's experts. Dr. Drew Schwartz is an Assistant Professor and Physician Scientist of Pediatric Infectious Diseases at Washington University School of Medicine in St. Louis, Missouri. His laboratory is focused on the gut microbiome in serious bacterial infections. Dr. Aayushi Uberoi is an Assistant Professor in the Department of Pathology and Immunology at Washington University School of Medicine in St. Louis. She focuses on host microbiome interactions in the response of skin epithelia to injury, skin diseases, and environmental exposures. And we'll put this first question out to both of you. Can you please describe the current state of microbiome-based diagnostics in clinical medicine? Dr. Schwartz, let's start with you.

Drew Schwartz: Sure. I think this is a really exciting and new area that has been coming forth into clinical medicine lately. I think one of

the first things that we do need to address or ask about is what we mean by the microbiome. Some people will refer to that meaning collection of organisms in a specific location, like the gut that I study, or the skin, like Dr. Uberoi studies. But it could also represent areas in which there are nucleic acids from organisms without their presence. So some of the common potential microbiome spaces include the blood or cerebrospinal fluid. And there are certainly diagnostics through University of California, University of Washington in Seattle, as well as companies such as Karius that'll take sites from the body and try to identify nucleic acids to identify a missed infection that couldn't be captured by culturing.

Then the next question is, in a place where bacteria are supposed to be, like the gut or the skin, is there any role for microbiome diagnostics or profiling? I think that is certainly coming to the clinical space, but for right now, it's mostly just in the setting of, 'well, we'd like to understand what organisms are there, and at the next step, could we maybe do something about that?' But for right now, that's mostly in the research or the industry space, which is knowledge-based and not necessarily ready for clinical prime time practice.

Aayushi Uberoi: And I would like to echo what Dr. Schwartz said. I study skin microbiome, and one of the most exciting promises for microbiome diagnostics is actually in wound infections, which are actually a huge clinical burden. But we literally began to scratch the surface so as to say, because in the context of wound infections, we're even at the research level determining what are the determinants of wound infections. But the promise of microbiome diagnostics is extremely exciting, and I'm hoping that in the next decade, we will make huge leaps in that space.

Bob Barrett: Doctors, how does the public perceive microbiome-based diagnostics, and what are some of the misconceptions?

Aayushi Uberoi: So, this is a very fascinating and very important question. Microbiome has become the new buzzword so as to speak. And as much as we as researchers love what we do, and we're absolutely excited about public's knowledge about microbiome, sometimes what happens in the term of communication of findings is that the relation between causality and correlation is often missed and the nuances are often overlooked. So, for example, in some cases, people may assume that we have found a particular microbe that indeed is, like, ready for clinical application when we have actually only started studying it. So in the context of public perception, sometimes things get over-sensationalized.

And now, because of social media, everyone seems to think that we have found probiotics for skin care, for example, whereas we're still trying to figure out some of those

fundamentals. That being said, this is extremely exciting in the context of science, that people have been so fascinated by the microbiome, and I think that comes because it is so personal. For example, in the skin and the gut, we know that there's interpersonal variation among individuals, and a lot of it does rely on nutrition. So, it is very exciting that the public is excited about this realm of research, because that brings to us funding and more attractive opportunities. But with all science, we need a bit of careful understanding of how to interpret some of those findings.

Drew Schwartz: It is very exciting certainly, as Dr. Uberoi said, that everybody is interested these days. But I think it really takes a bit of patience and pause to understand that we're still in the nascency of this. This is not something where we have identified specific individual infections and we've isolated them from people's bloodstream and then we can put them into animal models and prove that they cause an infection and then take them out. This is termed Koch's postulates to identify an infectious disease. Right now, this is, as Dr. Uberoi said, these are associations. And at best what we can do right now is to say your gut microbiome doesn't look like what we call a healthy human's gut microbiome. But jumping that next step from how do we ameliorate that versus teasing apart is this just correlated with your diet, your environment, et cetera, I think is the next step. And it's really not yet ready to be the key diagnostic that people want it to be.

The other approach or the other thing there is that this is not a one-size-fits-all approach when it comes to, say, remediating microbiome damage with something like a probiotic. There's tons of these companies that have probiotics on the shelf for picking up. And yeah, it's probably not going to do a lot of harm, but this is a very personalized thing. And if we're everybody using the same exact probiotic, the same exact bacteria, that's probably not going to be the solution to everybody's health problem, even if it is causally related to the gut microbiome or a microbiome in another space.

Bob Barrett: So, what is the current status of probiotics?

Drew Schwartz: Yeah, so that's a very good lead in, which is there are tons of probiotics available on the market, individual organisms, consortia of organisms. And it's a very popular thing for people to want to take probiotics for whatever reason. So, let's say you think that you're lacking a specific organism and you would take it. In the absence of microbiome disruption, it's really uncommon for those organisms to be able to gain a foothold in this complex environment that is very well established at homeostasis. The other part is that people want to take them when they're either on antibiotics or after being given antibiotics. There's a couple of issues or a couple

of considerations to have. One is that when you're on antibiotics, it's possible that the probiotic that you're taking is going to be killed by that antibiotic that you're on. The second thing is, let's say we want to use it for recovery after antibiotics. And again, I go back to the personalized approach, which is it's probably not the right probiotic for everybody.

And there's a great research paper from the Elinav group where they took healthy adults. They gave all of them IV antibiotics, and then they randomized them to three groups: one group that was given their own microbiota back immediately after antibiotics; one group that was allowed to spontaneously recover, just go back to their normal routine; and the third group was given a probiotic consortium. The group that got their own microbiota back after antibiotics immediately recovered to their pre-antibiotic baseline. So that was great. The group that had spontaneous recovery, in about three weeks, they looked like their pre-antibiotic baseline. The group that got probiotics never returned to their pre-antibiotic baseline. Now, you could say that was great, because we knew exactly what we were doing and we knew the key microbes that their gut microbiome needed, and we added those. But if we don't have all of the information and we give people an organism that might not fit in that environment or might not contribute the desired functions, then it could cause harm. Again, it's probably unlikely, but this is just a very complicated environment that we're disrupting and not allowing to return to its baseline.

The other area where, from my own practice it's important, is in neonatal intensive care units, where a lot of babies are in close proximity, and bacteria are shared among individual babies and their surfaces. So let's say baby A gets a probiotic, it ends up in the stool of other babies in that same environment. And again, if we don't know what we're doing in each of these individual human babies and these individuals, then it's probably not the right approach for a one-size-fits-all probiotic.

Aayushi Uberoi: Following up on what Dr. Schwartz spoke, in the context of skin, there have been a lot of products which have gained a lot of attention in the last few years, which are called skin probiotics, which is actually a very complicated thing in the context of skin. So, in the context of skin microbiome, the field is more at infancy compared to the gut microbiome field, for starters. For example, what we know at this point is that even on the skin, at different sites, we have different general microbiome communities. So, for example, the microbiome on the forehead looks completely different from the microbiome on the nose, and that has a lot to do with how the structure of the skin is. So the fact that one probiotic could fit all is immediately sounding wrong.

The second aspect is, in the context of skin, we at this point don't even know what is the best way to introduce probiotics. So, for example, the skin is what we can almost perceive as a desert, that there is less nutrition for the microbes to even thrive. And we're really only beginning to understand the ecology of the skin in terms of what the bacterial composition is. So for most part, at least in our hands, in the lab settings, when we do try to introduce probiotics, supposedly on the skin, they're actually not even able to colonize because they're out-competed or do not have the nutritional requirements to even thrive on the skin. So in the field of skin research, although probiotics is something which is super exciting, we're still pretty far from actually having probiotics. A lot of probiotics that are currently out there for skin are largely in cosmetic realm, and almost all of them do seem to be similar to the gut probiotics that are used, which I'd like to bring to everyone's attention, that actually all these organs have very distinct microbiome compositions. So microbiota that we know live in the gut usually are not the same as those on the skin. What is exciting is that we have all these amazing research possibilities, and we expect that this will change over time. But at this point, we're a little far from having a perfect skin probiotic.

Bob Barrett: Well, finally, doctors, let's look ahead. Where do we go from here with this research?

Aayushi Uberoi: One of the most exciting possibilities now with the advent of next-generation sequencing, which is just literally improving day by day, is that we can actually address some of these complexities in terms of the microbiome. So we have mostly been focused on studying species level compositions. But within the species, there are strain level compositions of the microbiome, which are actually thought to be even more informative and more biologically significant than some of the species variation, so that is something that we would be able to address. In the context of skin, what would be very interesting is, I already alluded to this previously, that the structure of the skin itself is extremely complex. What looks like a flat surface to us is actually not a flat surface. It is inundated with hair follicles, pores, or as pilosebaceous units, as we refer to them, and sebaceous glands. And these have their own architectural niches. So also, with the advent of modern technologies, we can resolve these microbiota more spatially.

The other aspect, which is going to be super important and exciting as we move on, is actually a lot of microbiome research has been focused on bacteria. However, microbiome consists of different species, such as viruses, archaea, *Proteus,* and so on. And what we hope, as our sequencing technologies are becoming really awesome, is

that we will be able to also understand these other kingdoms of microbial contribution to the microbiome research. So, these are some of the aspects that I'm very excited about that can help us understand and delve into more personalized microbiomes. So, one thing which I hope came out of the discussion today is that one size does not fit all. And I think with our further efforts, we'll be able to come up with more personalized interventions, taking a more holistic approach in approaching some of our research questions.

Drew Schwartz: I completely agree with what Dr. Uberoi said, and I think it's a really exciting time to be in the microbiome space. I think one of the issues that we have is that these diagnostics are often not rapid.

And in order to get these types of tests to the clinical space, they need to be very quick. You can't have somebody who has, let's say, a serious infection or is undergoing some sort of inflammatory process, and then three to four weeks later, you get their gut microbiome results back, or their skin microbiome results back. So, one of the really exciting things is companies such as Oxford Nanopore, who've identified sequencers that are fairly cheap, can fit on a USB flash drive, and can give you what's called long-read sequencing within a couple of hours, up to 24 hours. And this has the potential to revolutionize clinical medicine because you could identify key differences from whatever baseline if you were to do longitudinal sampling on an individual, or when we get enough data to identify differences from a "standard," whatever that means, and then rapidly identify the problem, and then try to come up with whatever amelioration strategy you have, whether that's antibiotics to kill certain organisms, phage therapy, which is a type of virus that can specifically target bacteria, antifungals, because as Dr. Uberoi mentioned, there's fungi in the microbiome.

So, I think the next step, from my perspective, is getting this stuff from less of a, 'well, let's just see what's going on,' to more of a rapid, quick diagnostic that can then lead to rapid treatments to resolve some of these conditions that are definitely linked to gut microbiome problems or skin microbiome problems.

Bob Barrett: That was Dr. Drew Schwartz and Dr. Aayushi Uberoi from Washington University School of Medicine in St. Louis, Missouri. They served as content experts for a Q&A article on microbiome-based diagnostics in the June 2024 issue of *Clinical Chemistry*. And they have been our guests in this podcast on that topic. I'm Bob Barrett. Thanks for listening.