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*Clinical Laboratory Testing and Metabolomic Approaches for Donor Screening, Product Assessment, and Patient Monitoring.*

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**Guest:** Dr. Nirja Mehta is an assistant professor in the Division of Infectious Diseases at Emory School of Medicine in Atlanta, Georgia.

Bob Barrett:

This is a podcast from *Clinical Chemistry*, a production of the Association for Diagnostics & Laboratory Medicine. I'm Bob Barrett. *Clostridioides difficile*, or *C. diff* as it's more commonly known, is a significant health challenge as it disrupts the healthy gut microbiome, leaving patients with intractable diarrhea or even severe colon damage. Further complicating the problem, antibiotics used to treat these infections further deplete the gut microbiome, opening the door for recurrent *C. diff* infection.

In these cases, further rounds of antibiotic treatment are not the answer. But what strategies do we have to restore microbial balance and break the cycle of recurrent infection? Enter the fecal microbiota transplant. This treatment is safe and effective, but after the largest commercial supplier of transplant products stopped distribution, institutions became dependent on local stool biobanks.

Like any transplant program, extensive checks in the form of donor screening and product testing must be performed to ensure safety for the recipient and a successful treatment outcome. However, since this is a relatively new field, best practices are a work in progress, offering an exciting new opportunity for laboratorians to make meaningful contributions to patient care. A new review article in the May 2026 issue of *Clinical Chemistry* discusses the field of fecal microbiota therapy, with a particular emphasis on clinical laboratory contributions to donor screening and product evaluation.

Today, we welcome one of the article's authors. Dr. Nirja Mehta is an assistant professor in the Division of Infectious Diseases at Emory School of Medicine in Atlanta, Georgia. She studies the role of the gut microbiome in infectious diseases, with a particular interest in *C. difficile* microbiome therapeutics. So, Dr. Mehta, just what is fecal microbiota transplantation and why do we use it?

Dr. Nirja Mehta:

Yeah, absolutely. So, we have a little bit of a diverse audience and an international audience. So, I'm going to speak a little bit about how it's used medically and then a little bit about some regulatory things as well that sort of impact its utility

as well. Fecal microbiota transplantation is a process by which whole stool is taken from a human stool donor. It's screened, both the donor is screened and the stool itself is screened, and then sort of minimally processed and then implanted into a recipient with some kind of pathology that we think would benefit from resetting the gut microbiome, so to speak.

The therapy is most commonly used in the prevention of recurrent *C. difficile*, *Clostridioides difficile* infection, which is a diarrheal infection that's healthcare associated. And it's also a part of the therapy for patients who have what we call fulminant *C. diff*, so very critically ill patients who are suffering from the *C. difficile* infection. That is the most common use of this particular therapy because it is the most well-studied.

However, there's increasing interest in leveraging this therapy for a variety of other conditions in which we think that what I like to call 'hard resetting' the gut microbiome may be beneficial. There are studies and experimental uses of fecal microbiota transplantation, also known as FMT, in everything from inflammatory bowel disease to diseases that are linked with things like the gut-brain axis, for example, so Parkinson's or mental health disorders as well. So, it is a therapy that is most commonly used in *C. diff* but can be used in a variety of other things as well.

Bob Barrett: How has access to FMT product changed over the past 10 years in the U.S. and how does this compare with the rest of the world?

Nirja Mehta: One kind of interesting thing about FMT is that historically this was sort of the mainstay. In 2013, we had the first randomized control trial which demonstrated efficacy in the use of fecal microbiota transplantation in preventing recurrent *C. diff*. And so, from then on, it was a mainstay of therapy both in the U.S. and then increasingly abroad as well.

However, in the United States in 2024, the large biobank that provided product, so they screened dual donors and they distributed the product, stopped distributing product. And so, as a result of that, most institutions, healthcare institutions in the United States, lost access to this particular therapy. Outside of the U.S., there are a variety of ways in which institutions, academic institutions or medical institutions, acquire products. Sometimes these are through national biobanks, sometimes these are through academic centers which sort of act as distribution centers nationally. And so, access to this therapy varies significantly based on where patients are geographically located. One of the reasons that it has changed in the United States is also with the advent of new microbiome therapeutics.

So, we have two new FDA-approved products which are fecally-derived microbiotherapies, which are sort of superseding the use of FMT, but both of these are more expensive. And so there is still a very great interest in evaluating whether FMT needs to be brought back, potentially even on an institutional level, as an option for therapies in certain patients.

Bob Barrett: Doctor, what are the current recommendations for FMT donor screening?

Nirja Mehta: Yes, so just to kind of reiterate, an FMT donor is going to be a person who is healthy, who has what we would think of as a nice, diverse gut microbiome, and therefore would be eligible to donate their stool to someone who has what we call dysbiosis of the gut microbiome, so an imbalance in the good bacteria in the gut microbiome that we are trying to reset or reintroduce good bacteria to.

The donor screening protocols vary somewhat, but in general what happens is that patients are screened with blood tests to look for major infections such as HIV, hepatitis, viral hepatitis, syphilis, and a variety of other things. And then the stool itself is screened for infectious diseases, as you can imagine. So, we of course are going to screen for *C. difficile* itself. It would be counterproductive to transplant *C. diff*-positive stool into somebody who we're trying to eliminate *C. diff* from, as well as *Giardia*, *Cryptosporidium*.

And then there had been a lot of, or a few incidents of multi-drug-resistant organisms being transmitted via fecal transplant, and so that's another thing that we're very careful to screen for via culture to make sure that we are not transmitting drug-resistant enteropathogens, so drug-resistant *E. coli*, for example, from donor to recipients.

One thing that is worth noting, though, in spite of all of these screening mechanisms that we have, all of these are to evaluate the safety of the procedure, but they don't actually evaluate necessarily the quality of the product, right? So, as you can imagine, stool is sort of notoriously heterogeneous. Every single person has a very different stool microbiome based on their environment, based on a variety of other things.

Even healthy people have a variety of different stool microbiota, and so one of the kind of holy grails of fecal microbiota transplant study is to try to evaluate whether the stool that we are actually going to transplant into a person will result in microbiome changes that are actually desirable, and that's something that is kind of interesting to see whether we can leverage things like metabolomics, metagenomics,

things like that to actually evaluate whether the bacteria that are actually in these stools, even if they're from healthy people, are really the desirable ones that will help patients avoid different medical conditions that we're trying to accomplish.

Bob Barrett: What stool metabolites are commonly measured in microbiome therapy, and should these metabolites be routinely evaluated?

Nirja Mehta: Yes, so in experimental studies, there's a lot of interest in evaluating a variety of different markers of what we call bacterial engraftment, as well as the level of gut microbiome imbalance in the pre- and post-FMT states. However, historically, none of that has been an important component of evaluating stool itself, so when we take stool from healthy donors and implant it into recipients, what we're really just looking for is, 'Is this a healthy person who is likely to have a nice, diverse gut microbiome, and are there any communicable diseases that we're concerned about here?'

However, increasing experimental design demonstrates that metabolites--so these are products that are made either by the bacteria itself in the gut microbiome or by cells themselves in the microbiome--do play a major role in, for example, *C. difficile* pathogenesis, and the most illustrative example is bile acids. So primary bile acids are made in the liver, and they traverse to the gut, and they're hydrolyzed by gut microbiota, good bacteria that live in the gut.

And so, we know that the ratio of primary versus secondary bile acids in the gut is sort of a proxy for the amount of good bacteria in the gut. And we also know that primary bile acids are a major driver of *C. difficile* pathogenesis, and so in patients who have a large number of primary bile acids in the gut, they're more likely to proceed to full-blown *C. difficile* infection.

And so, this is a metabolite that is valued and measured in a lot of novel microbiome therapeutic studies. So, if you look at, for example, the phase 3 study from the product that is now called VOWST (fecal live-brpk), they evaluated the ratio of primary and secondary bile acids pre- and post-treatment and noted that that change seemed to correlate with how well the patient responded.

And so, there's a discussion about whether looking at metabolites such as bile acids would be productive pre- and post-implantation and evaluating whether the number of fecal bile acids that are in the donor product may be a productive way to evaluate whether this would be something that would be beneficial to the patient. There are a lot of other metabolites, such as short-chain fatty acids, Stickland

metabolites, acetylcarnitine that also play a role in *C. difficile* pathogenesis, but the water on that's a little more murky. So, I'm going to say those are probably not as ready for prime time as bile acids may be, which are fairly well established as being important in *C. difficile* pathogenesis.

Bob Barrett: Well, finally, Dr. Mehta, is there a role for metagenomic analysis in screening donor stool for FMT?

Nirja Mehta: This is really interesting, right? Because you would think so. You would think that it would be really helpful to know the exact composition of the donor stool and the exact composition of the recipient and try to find this perfect puzzle piece of this is what's missing and this is what needs to be added. But unfortunately, our technology and our understanding of stool engraftment, is just not at the point where I think that we're necessarily able to reliably do this.

So, I think that this would be a great application in the future once our understanding of strain engraftment, of how bacteria, when they're introduced to a particular environment, take hold versus don't. But at this point, I don't think so. But I think that it's worth noting that there's a lot of signal to say that this may be where the field is going in the future. For example, we know that following FMT, there are positive clinical outcomes correlated with increased Firmicutes and Bacteroides species in the gut and a decrease in Proteobacteria and Enterobacteriaceae.

But does that necessarily correlate with those ratios in donor and recipient stool? And that's not entirely clear right now. It does seem that this is somewhat disease-dependent as well. We spent the majority of this podcast talking about the use of FMT in *C. difficile*, just because it's the most common use case. But there's a lot of really interesting work, as I mentioned at the top of the podcast, and things like IBD, inflammatory bowel disease. And that seems to have a different set of bacteria that are keystone species. And so, I think that this is a very interesting direction to go in eventually, once we have a better understanding.

But I think right now, we're still at a point where we don't know, for example, what the minimum abundance concentration that would be acceptable would be. We don't really have standards. And so, putting this into the clinical space at this point, we're not quite ready for that. But I do think that it's a really interesting place for scientists to explore so that we can make those kinds of standards in the future.

Bob Barrett: That was Dr. Nirja Mehta from Emory School of Medicine in Atlanta, Georgia. She wrote a review article in the May 2026 issue of *Clinical Chemistry* on fecal microbiota therapy for

recurrent *C. difficile* infections, and she's been our guest in this podcast on that topic. I'm Bob Barrett. Thanks for listening.