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Molecular Approaches to Transplant Monitoring; Is the Horizon Here?

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Guest: Dr. Sean Agbor is a laboratory chief, a Lasker Clinical Research tenure-track investigator and at NIH distinguished scholar at the National Heart, Lung, and Blood Institute in Bethesda, Maryland. He is also an assistant professor of medicine at John Hopkins.

Bob Barrett: This is a podcast from *Clinical Chemistry* sponsored by the Department of Laboratory Medicine at Boston Children's Hospital. I'm Bob Barrett. Transplantation is a remarkable procedure that gives a second chance of life to patients with end-stage organ failure. Unfortunately, this exposes the transplanted organ, or allograft, to the recipient's immune system, predisposing the allograft to acute rejection, a dreadful complication, and a major risk factor for allograft loss. To preserve the allograft's health, providers carefully monitor their patients to maintain immunosuppression adequacy carefully balancing the risks of rejection and infection. Monitoring approaches vary substantially among providers and transplant programs.

Fortunately, in the last few decades, novel molecular approaches have been introduced showing promising results with benefits that address the limitations of biopsy and conventional histopathology. In a Q&A feature appearing in the November 2021 issue of *Clinical Chemistry*, five experts discuss the potential utility of these novel tools to monitor solid organ transplant patients. The moderator for that Q&A feature is Dr. Sean Agbor, a laboratory chief, a Lasker Clinical Research tenure-track investigator and at NIH distinguished scholar at the National Heart, Lung, and Blood Institute in Bethesda, Maryland. He is also an assistant professor of medicine at John Hopkins, and he is our guest in this podcast. So first of all, Dr. Agbor, what are the special needs to carefully and frequently monitor transplant patients?

Sean Agbor: Transplantation, as you know, is a wonderful treatment wherein patients who have organ failure receives a new organ and a chance to live again. What a wonderful treatment. However, when you put that organ in a different person, the recipient of that organ have an immune system and that immune system recognizes that organ as foreign. And so they'll have to mount antibodies and other immune pathways to reject that organ. Therefore, we need to give this patient immunosuppression medications. We have to titrate the dose of the immunosuppression medication to prevent rejection, but not to reduce the immune system so much as to predispose this patient to infection. Therefore, transplant

patients need careful monitoring to balance their immunosuppression to prevent rejection while avoiding infection.

Bob Barrett: One of the topics covered in this Q&A feature on molecular approaches to transplant monitoring is use of cell-free DNA to monitor transplant patients. How appropriate and clinically accurate are these procedures?

Sean Agbor: So cell-free DNA is truly becoming a state of the art blood test to monitor patients for transplant rejection when compared to the traditional method, which is biopsy. If you think about biopsy for a minute, you have to go into the patient and take out a sample of the transplanted organ whether it's the kidney, the liver or the lung. That is such an invasive procedure. Patients don't like it and it takes so much time. Cell-free DNA is a blood test. All the patient need is a blood draw and in that blood draw you can then measure DNA that's coming from that organ called donor-derived cell-free DNA as a measure of injury and transplant rejection. There have been a multitude of studies that have been published in the last decade or so demonstrating that cell-free DNA is quite sensitive and detects rejection sometimes earlier two to three months earlier than biopsy. So that's the preliminary data. There are ongoing studies now that will show the true clinical benefit of cell-free DNA. We are waiting the results of those trials.

Bob Barrett: Another topic covered in this Q&A article is the molecular microscope. What exactly is that and how well is it suited for transplant monitoring?

Sean Agbor: This is an approach that is gaining significant steam. With this approach, a biopsy sample is obtained from the transplanted organ. And rather than looking at the biopsy on a microscope like we do traditionally, we look at that biopsy on a molecular level, looking at RNA and other transcripts to inform us what's going on. So this method is quite detailed because we're not looking at the microscope rather we are looking at the biopsy sample at a molecular level.

It makes it therefore quite detailed, and this emerging data indicating that this molecular microscope is quite good at picking up rejection. Indeed, emerging data is showing us that this molecular microscope approach can actually redefine the way we consider rejection. Some of those studies to also show its clinical utility, it's ongoing. The molecular microscope, however, requires biopsy. Still requires you to go into the patient to get a sample, but it also offers all this added approach, all this detailed molecular level examination of these tissue samples to not only tell you about rejection, but it can also give you certain clues into how best this patient should be treated. So I find it a quite useful approach as well.

Bob Barrett: In addition to monitoring, are there potential future applications of these tools to improve transplant care?

Sean Agbor: I think there are quite a few at least the preliminary data is showing us. Let me start with cell-free DNA. We can use cell-free DNA, I think the clinical studies would support this, that we can use cell-free DNA to monitor patients because it is a blood test. You can sample the blood from these patients quite frequently, so it's likely going to give us a better resolution of how frequently we can monitor patients. Number two, can we use cell-free DNA as a measure to say a patient is adequately immunosuppressed? Currently, when we give our patients immunosuppression drug to prevent rejection, we measure the levels of the drug in their blood. That is a very inappropriate measure for some patients because some patients have good levels of drugs but still go on to have rejection. Can cell-free DNA be used as an adjunct in addition to this monitoring of drug levels to see whether the patient is adequately immunosuppressed?

Those are some future studies that are coming up. On the molecular microscope side, in addition to detecting rejection without a lot of variability between operators, as is the case with traditional biopsy and microscopy, I think the molecular microscope can help us redefine rejection. Let me give you this example. Take a case of a patient who has a type of rejection that we call antibody mediated rejection. This is rejection that's mediated by antibodies. If you look at lung transplant patients who have that diagnosis of antibody mediated rejection, if you treat them for rejection, only about 20% to 25% of those patients will respond to treatment and their lung function will improve. The majority of them will not. They'll go on to show progressive loss of their lung function, ultimately dying within two to three years. The question becomes, do these two patients have the same disease? If so, why do they respond differently to treatment? My hope is that two such as the molecular microscope can begin to redefine how we call these diseases such that it can inform us into exactly at the molecular level what is happening and hopefully we can then pick up effective treatment to treat these patients. These are things that I think may happen in the near future with these tools.

Bob Barrett: Finally, doctor, with all of the discussions from experts around the world, what are your take home messages to share with our listeners?

Sean Agbor: I think I have to really thank the editors of *Clinical Chemistry*. This has been a wild and tremendously beneficial experience for me personally. However, in the scientific community, I think it is a truly brilliant idea and please allow me to extend my congratulations to the editors who are thinking about such

an approach. I have noticed that there are brilliant scientists truly across the world. If only you look, you would see them there. And this experience to try to sample opinions from across the world enabled me to go online and look at work that is being done in this truly challenging field of transplantation. I was amazed by what I found. Starting all the way from Australia, China, Europe, the US, South America, and Africa. It's been an amazing experience trying to sample these opinions from around the world that enables you to see just how much these scientists across the world are contributing to this field.

And so for that, I truly like to congratulate the editors of *Clinical Chemistry* for thinking about this approach of synthesizing science in this field.

Bob Barrett: That was Dr. Sean Agbor from the National Heart, Lung, and Blood Institute in Bethesda, Maryland. He served as moderator of a Q&A feature on New Tools to monitor solid organ transplant patients. That article appears in the November 2021 issue of *Clinical Chemistry*. I'm Bob Barrett, thanks for listening.