Dr. Sean Agbor-Enoh

Behind the Mask Interview

October 8, 2020

Barr: Good morning. I'm Gabrielle Barr of the Office of NIH History and Stetten Museum. Today I have the pleasure of talking to Dr. Sean Agbor-Enoh who is a tenured track investigator at the National Heart, Lung, and Blood Institute (NHLBI) as well as a physician at Johns Hopkins [Hospital]. Thanks so much for speaking today with me for our Behind the Mask Project.

Agbor-Enoh: Thank you for inviting me.

Barr: Recently you received a grant to study early cell-free DNA profiles to predict COVID-19 clinical trajectories. Can you talk about, in lay terms, what influenced you and your team to look at this particular subject?

Agbor-Enoh: Thank you, Gabrielle. That's an important question. I am a pulmonary physician who specializes in lung transplantation and we work on cell-free DNA. We've been familiar with that molecule. So, when COVID-19 came early this year, I was looking at TV just seeing what's happening in New York. The ICU beds were full. They were all out of capacity. I suspect that it was very difficult for healthcare managers to plan to resources, how can they anticipate patient who will need the ICU versus patients that will not need the ICU OR patients will have bad outcomes from COVID-19 compared to patients who do not. So, I said, "If only there was a test that would help healthcare providers anticipate that this patient will need the ICU, this patient will need the ventilator. Then they may be able to better plan how to manage health care resources." That's what gave us the idea to say, "Could we use cell-free DNA to do that because our experience in transplantation has shown us that in patients who develop transplant rejection, if you use cell-free DNA, you can pick up transplant rejection two to three months before the patient shows any signs of rejection." Therefore, if you bring that to COVID-19, can we pick up patients who become very sick and need the ICU earlier than they will get there?

Barr: Can you describe because I think some of our audience may not know what cell-free DNA is?

Agbor-Enoh: Yes, cell-free DNA is a DNA molecule, as the name says is cell-free, so it's a DNA molecule that's out of a cell. As you know, normally in every cell DNA is only inside cells. That's how we learned it in school and that's how it is. When that cell dies, the content of that cell is released. Part of that content is the DNA that's part of the cell.That DNA then ends up in your bloodstream. We can now get a few drops of your blood to sample DNA coming from everywhere in the body where cells are dying. That is cell-free DNA. It is a DNA molecule that has been released from a cell that is dying. Therefore, the

amount of cell-free DNA that you have, gives us a sense of how many cells are dying. The more cell-free DNA you have, the more cells are dying. That means you're not in good shape if you have high cell-free DNA. It's not a good thing; you're not in good shape. If you have lower cell-free DNA, you're in better shape than if you have high cell-free DNA.

Barr: Interesting. What is the process that is used to create this cell-free DNA?

Agbor-Enoh: Cell-free DNA is released from the cells as part of the contents when the cells die. So, when something is wrong like someone gets the COVID-19 infection so the cells will be dying at a higher rate than someone who does not have a COVID-19 infection. The person with this infection would therefore have a higher cell-free DNA than the patient without an infection.

Barr: So that's how cell-free DNA is produced. That's very interesting. So, with your experiment how are you determining that the amount of cell-free DNA in your sample population is not indicating another condition, because you said that it can signify organ reduction or precancer or other situations?

Agbor-Enoh: As of now, the technology that we have is not the best at distinguishing one situation from another. It's only good at telling us that something is wrong, or something is very, very wrong. It can tell us that and then now, as a clinician or as a doctor, you can now go on to figure out what is wrong. That's one big advantage, so it tells us what is wrong, and it tells us how bad it is. Not only that, it can tell us weeks to months before it happens. So, if someone is going to need an ICU from COVID-19 infection maybe next week, can the test tell us today that this guy which looks fine now may need an ICU next week? That's what we think it would tell us for COVID-19. For transplant, that's what it tells us. It says this patient is going to have a rejection in two to three months if you don't do anything. This will allow for better data planning. If you think about lung transplantation, half of the patients die within five years of receiving the organ because they develop transplant rejection. What if a doctor can pick up the transplant rejection and I treat it early; will those patients still go on to die? Not clear whether that's the case. Not only the fact that it picks up early, it also enables us to treat the disease earlier and maybe treating the disease earlier may be beneficial compared to if we were to wait.

Barr: How are you selecting your sample population?

Agbor-Enoh: For now, we've started by just picking patients that have tested positive for

Sars-Cov-2, which is the virus that causes COVID-19. When the patient tests positive, we would approach the patient and we would recruit and enroll the patient. We collect blood samples from the time closest to their testing and we collect blood samples serially after that until the patient ends up in the hospital, in the ICU or, for some patients unfortunately, until they die. We collect those serial

samples so we can understand the differences in cell-free DNA trends between patients with COVID-19 that have different degrees of disease severity. That's where we are now. Down the road, we're going to collect samples from patients with other viruses so we can see how COVID-19 differs from other viruses. We'll do that, but we've not started that yet. Now only patients who have tested positive for Sars-Cov-2. We collect samples from them.

Barr: Have you already made any observations so far among the people you've tested?

Agbor-Enoh: Preliminary, so preliminary. It's not been published yet. This is information that we still need to do additional work to see if this is the case. So, number 1, we've set up a study to collect samples from these patients at four U.S. hospitals: Johns Hopkins in Baltimore, University of Maryland Medstar hospitals, and Inova Fairfax hospital. We're also setting up the study to collect samples in two international countries: one center in Cameroon, which is in Central Africa, and another center in Kenya, which is in East Africa. So, in total we would be receiving samples from six different centers and from three different countries.

So far, the study has started in U.S. centers. We have about 190 patients that we've collected samples for. We've collected a total of around 950 samples from all these patients and we've brought the blood samples to our lab and have done some preliminary work on about 200 of those 900 samples. The preliminary work shows us that, if you compare patients who have COVID-19 with healthy controls, the amount of cell-free DNA is a hundred times higher than for people who are healthy. I have not seen that amount of cell-free DNA; I've never seen that high an amount. It's unbelievable! Which tells me that this virus is not just bad because it kills people the way it does, it's just simply bad a hundred times more than in healthy controls. That is just a very big number and so as we've done this, it seems like that is the case.

We've done this from samples from Maryland. Okay, maybe it's just one hospital. We've changed and we've gone to another hospital, Johns Hopkins, and the findings reveals the same. We've gone to Inova Fairfax hospital and again the same. It seems like across all these different hospitals where we get patients, the patients with COVID-19 just have very, very high cell-free DNA. What this tells us is that COVID-19 is causing a lot of tissue damage.

That's the first finding we have. The second finding that we are beginning to see on a small subset of patients that we analyzed is that for the patients who end up in the ICU, the amount of cell-free DNA is also higher, about five to ten times higher, than for the patients who do not end up in the ICU. That's really interesting, so those are preliminary. Hopefully, we'll do more work to get to finally figure those things out.

Barr: What kind of tools and applications and other kinds of programs are you using to conduct your study?

Agbor-Enoh: We do a lot of gene sequencing as you can imagine. We take plasma samples; we isolate DNA; we isolate RNA; we isolate different things; and then sequence it. A lot of our stuff is done by gene sequencing. We use some cutting-edge approaches to be able to identify DNA that's coming from different organs, for example, the DNA from the heart looks different from the DNA from the lung.

Barr: I didn't realize that.

Agbor-Enoh: Oh yes. DNA has things on top of it. If you think about DNA as being a Christmas tree and the Christmas lights are additions on top of the Christmas tree, so DNA has additions on top of it called epigenetic markers. So even though in the same person the DNA sequence is the same in the heart, in the lung, and in other organs, the epigenetic markers are different. Therefore, your DNA coming from your heart have epigenetic signatures that are different from the DNA coming from your lung, from the DNA coming from your kidneys. Therefore, with a few drops of blood you can almost draw a map of cell-free DNA from the entire body—how much is the kidney being injured, how much is the heart being injured? So, you can draw a body injury map.

Barr: That is really interesting.

Agbor-Enoh: That's where we're going with COVID-19: to say which tissues and organs from all over your body are being injured. Then can we use that map to say whether that patient may need the ICU or not. Well, that patient may survive or not. Not yet. That's where we're going now.

Barr: It's very interesting. I can imagine that your study has a lot of people involved. Can you discuss what your role is?

Agbor-Enoh: I am the principal investigator, but I have been fortunate to find wonderful collaborators and also wonderful people in the lab. Now collaborators, as I just said, we have studies recruiting patients at six centers, four in the U.S. and two international centers. At each of these centers we have identified and have a collaborator there who is simply phenomenal in recruiting these patients and collecting samples. So those are collaborators out there and each collaborator, you can imagine, have a whole group of people helping them to do this.

Those are the extramural and intramural collaborators. If you come internally, I have a nurse coordinator who helps to coordinate a lot of these different things. Then we have people in the lab that do the lab work.

My role as a PI is more to ensure that all these components are functioning well. You know we've thought about the study and we know where we're going. I think about my role which is to point to a mountain and say, okay, guys, I like us to climb that mountain, but there's no way I can climb that mountain alone.

Barr: Right. It takes a lot of people to do it. Can you envision how long you think your study will last ?

Agbor-Enoh: I suspect that within the next three to six months we will have a clear understanding whether or not cell-free DNA can be used to identify COVID-19 patients who will need the ICU. All of that I think we will be able to do. I also think though, that the way research is, that those findings that we'll see in the next three to six months or a year, it would open up other questions that we may need to answer.

For example, you know for COVID-19 for every 100 people that are infected with the virus, only about 20 to 30 of them will ever end up in a hospital. Seventy of them have only mild symptoms and they stay home. Why is that? That's very intriguing. So, I feel we would open up more questions where we try to seek more answers, if you may, to try to get a better understanding of why the disease affects different people so differently.

So, do I know when that research will end? The truth of the matter is I don't know. I think in about three to six months we'll begin to get a clear sense whether cell-free DNA could be a good test where, if patients are getting their COVID-19 testing, then we can take some blood samples to also do some cell-free DNA analyses. We can now predict and say, Oh, this patient may need to be in the hospital in a week, this patient may need ICU in a week or in two weeks and so forth, so to be able to tell someone with some degree of accuracy what will happen to this patient.

Barr: In addition to your role at NIH you are also a physician at Johns Hopkins. How has your job as a lung physician influenced your research? Can you speak a little bit about your two very different but intertwining experiences? It's probably very different in a lab than being a doctor in a hospital at this time.

Agbor-Enoh: Before COVID, my research and my clinical work were very intertwined. I'm a pulmonary doctor and I see lung transplant patients in clinics. Our biggest concern as a lung transplant doctor is

rejection. It's the biggest concern for every transplant doctor and is the biggest concern for our patients as well. If you look at my research, my research is on transplant rejection trying to find better ways of diagnosing and picking up transplant rejection and that's what prompted me to do that research. Anyway, as a transplant doctor, you're worried about rejection. The methods that we use now are biopsy. They are not very good at picking up rejection. We think they pick it up late. Could there be a better way? And that's what led me to this research. So the practice in my mind was in the same area as my research.

Then COVID-19 came, and it caused everybody to take a pause. As a physician, we are all called to pitch in and put in a hand to take care of these patients. So, I pitched in in different aspects of the hospital to make sure that the hospital does well. My clinical work got deviated a little bit from my research. However, now it's starting to work on COVID-19 research and the clinical practice all together are aligned.

Barr: Do you care for any COVID-19 patients during the time that you are at Hopkins?

Aglor-Enoh: Just about one or two, not many. I wasn't part of the COVID team that's taking direct care of the patients. The way Hopkins worked this out is that they created a separate unit to take care of COVID-19 patients. The patients that come there would be sent over to that unit. The patients that I took care of were patients that came to the hospital before. I wasn't part of that unit that's taking care of the COVID-19 patients. The patients that we see are patients that came to the hospital for something else and they were not COVID-19. We didn't catch it right at the beginning. They were admitted to us and then from there we found out they had COVID-19. Then we transferred them back to their unit.

The second place that I've taken care of COVID-19 patients is more as a consultant at the NIH. The NIH Clinical Center had COVID-19 patients there. I am part of the pulmonary consult team at the NIH . We would consult on the patients that have COVID-19 and provide advice on how to treat them. I was not the direct physician taking care of them. I was more of the consultant giving out advice on how to take care of them. That has been my COVID-19 experience.

Barr: That's very interesting. Now, these are more personal questions. What have you missed most about your pre-COVID life and what has been a silver lining?

Agbor-Enoh: I can go on and on telling you COVID is a strange disease. I have not seen anything like this in my entire life. This is the first time we've had such a thing. We've had other pandemics—H1N1, Ebola,

the MERS viruses, also the previous SARS viruses. I don't think anything even came close to this. This is amazing how it has changed everything. We took a lot of things for granted. Take this interview for example, we would not be doing it by this video conference device. You'd be sitting straight across from me and we'd be talking. We took those things for granted, the human part of us that where you sit with someone, you can shake their hands, you can say hi, you can hear their voice. We took all that for granted. COVID-19 has taken those things away for us, but it gives you a pause. It does say what is really important. It makes us recognize now that we were just taking a lot of things for granted. I'm going to get coffee with my friends. I used to do it every day. We just walked and got coffee and said, "Oh, it's just coffee." I can't remember the last time I went with anyone to get anything. I miss that a lot.

Lab work has changed because you have to reduce the number of people in the lab. It has just changed a lot, almost every aspect of everything that we do, but I think to do that it has brought a silver lining. It's really giving us an opportunity to stop, to pause, to ask really simple questions. What is important? Sometimes we used to go to dinner with friends and we say, "It's just dinner now." You begin to see what matters. So, it has given me a silver lining. It has really given me the time to pause.

Barr: That's good. Think all of us feel that way. If you had a superpower that would get you through this time, what would it be and why?

Agbor-Enoh: It is a tough time. You turn on the TV—the number of people dying just keeps going up. I'm a physician. I'm a critical care doctor as well, and I'm a researcher. You're so powerless that people are dying every day. This is really your bread and butter. This is something you should be able to come up with things that can stop this. You don't. We have not. There've been quite a few treatments that have come up but nothing that has been a silver bullet yet. That is frustrating. If I had that power, you can guess exactly what I would do with

It—to come up with something that can guide us, to get rid of this pandemic though I cannot. It's unfortunate for me how many people have died. That's so unfortunate . I think we're gonna mourn those people for quite some time. It has given us a time to just rethink who we are. I think it has and that's not a lesson that we should underestimate. If I had a silver bullet. we would be getting a cure. I think we would all agree to that; we would all want that.

Barr: Thank you very much for speaking to me today. It has been very interesting to hear about your research. I wish you the best of luck.

Agbor-Enoh: Okay. Thank you and thank you for the invitation. I appreciate this.