Zoom In on **Dementia & Alzheimer's**

The Gut Microbiome and Alzheimer's Disease: Understanding the Connection
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Transcript of Zoom with Beau M. Ances MD, PhD, Daniel J. Brennan, MD Professor, Vice Chair for Faculty Affairs, Department of Neurology, Washington University in Saint Louis

NANCY KEACH: I'm so happy to see everybody. Welcome. Good morning. Good evening. Good afternoon. Thank you for attending today. I am Nancy Keach. Welcome to the 34th episode of BrightFocus Foundation's Zoom In on Dementia & Alzheimer's program.

BrightFocus Foundation is a US-based nonprofit that funds exceptional scientific research worldwide to understand and treat Alzheimer's disease, macular degeneration, and glaucoma. And this Zoom series, which many of you have seen before, is sponsored generously by Lilly, Biogen, and Genentech. Thank you, sponsors, for making these free programs possible. It's so great to see everybody. I love seeing everybody's faces.

So today's program is "The Gut Microbiome and Alzheimer's Disease: Understanding the Connection." And I'm absolutely delighted to introduce today's guest expert. Dr. Beau Ances is the inaugural Daniel J. Brennan, MD Professor of Neurology at Washington University in St. Louis and Vice Chair of Faculty Affairs in the Department. His laboratory has focused

on developing novel methods to assess changes in the brain due to neurodegenerative diseases. For the past several years, his laboratory has focused on the role of the gut microbiome in Alzheimer's disease and other neurodegenerative conditions. Dr. Ances sees patients. He is a researcher and a clinician with neurodegenerative diseases, including Alzheimer's disease, Down syndrome, Creutzfeldt-Jakob disease, HIV associated neurocognitive disorders, or HAND, and long haulers due to COVID-19. Dr. Ances is an author on over 600 publications and has been featured in a PBS documentary, Dr. Ances, welcome to Zoom In. We're glad you made it on time.

DR. BEAU ANCES: It's wonderful to be here. So wonderful to see you and everybody else here. Thank you for having me.

NANCY KEACH: It's our absolute pleasure. So I'm going to jump in because we have so many questions and so much to discuss. But Dr. Ances made a suggestion in his email to me-- this is our 34th episode, which I'm so delighted to say, but it's been a very long time since we reviewed some of the basics. So I'm going to give you an impossible task, Dr. Ances. Very high level in five minutes, we're going to do what we've covered in 34 episodes. Very high level, what is Alzheimer's disease, and how do we diagnose it? Just as a little refresher course. Where are we today?

DR. BEAU ANCES: It's great. Thank you, Nancy. And you've had some really amazing people who have given talks on this, and it's really a pleasure to be here. And also, with BrightFocus, I can't tell you how supportive and how much it makes a difference to not only the research that I'm doing, but actually young investigators throughout the United States, as well as the world. So thank you, thank you, thank you.

So Alzheimer's disease is one of those when we use this big umbrella term of dementia. It is the most common. So if you went in, and you were to ever place a bet on stuff, and you were thinking somebody has some significant cognitive changes, and you bet that it was Alzheimer's disease, you would be right about 2/3 of the time. And how it has been made as a diagnosis has really changed. And it's really changed even during my lifetime as a medical student, compared to what I'm doing right now

and seeing patients. So in the past, the only way we could really make a definitive diagnosis of Alzheimer's disease was to look at pathology, so when a person passed, and then look at these two hallmarks of the disease, something called amyloid and tau. We are all making amyloid, as we're speaking right now, and we're also making tau. But usually, it doesn't deposit. It gets flushed out. And there are ways that it's flushed out, including through sleep, that you've also had talks on.

What's so different about Alzheimer's disease is that in Alzheimer's disease, it actually deposits in the brain, and then it leads to changes in the brain. And we are needing to use different biomarkers to make a diagnosis of individuals. And so the way that we do that now is through either imaging studies, so a PET image. So that's taking positron emission tomography or spinal fluid measures, or even more recently, blood measurements to evaluate these changes in amyloid and tau.

What we're going to talk about today is the gut and its relationship with the brain, and how early and can the gut also serve. So looking at your stool, which my kids love, because I'd rather hear about poop emojis than brain emojis, that they're very interested in. It's an easy way to make a diagnosis. And so there are ways that you can see for other kinds of cancers. And the question is, could we make a diagnosis? And are there certain things that we can do to help protect because of this gut brain axis.

NANCY KEACH: That was really good version of a short description. Just quickly then, so what are the stages and the treatments? Again, very high level today. And I do want to let everybody know that BrightFocus is about to go to print with an infographic on all of the FDA approved treatments as of today. And we'll be updating that digitally, but that's going to be a free resource available to all of you, that we'll be happy to share, and we'll include it in our resource summary at the end.

DR. BEAU ANCES: So what we know right now is that there are currently two therapies that are out there that are currently being used to target amyloid. So as I said to you, that is probably the first marker that changes within the brain. And it's the earliest marker that changes within the brain and is one of the hallmarks of the disease. And so the idea is that there

are now therapies that are called mAbs, monoclonal antibodies. So when you see on those commercials on the TV, and it ends with the letters M, A, B, that stands for monoclonal antibodies. So these y-shaped things that bind to the amyloid. And I'm using real technical terms. Suck it out or take it away or remove it from the brain. And so the idea is that there are these now new therapies that are out there. We have to watch very carefully. So there are MRIs and other safety tests that we do in safety labs for those individuals.

Also, more recently, we've shown that exercise and a healthy lifestyle, and also even Mediterranean diets are also somewhat protective and can also push off the disease. All the stuff that we're talking about, all of those kinds of medications or therapies, they're not the C-word, not the cure word. They're holding back on stuff. And so they're reducing the progression of the disease. We don't have that magical bullet. I wish we did. I would be loving to give it to a lot of people, including my mom, but we don't have that. And so because of that, we are trying to look and think of new therapies and new ways to do this, and in particular, this gut-brain axis and gut dysbiosis. So changes in the gut could be very important and an easy way to modulate that.

NANCY KEACH: Carol asked in the chat, what about GLP-1 drugs? And I'm just going to say to Carol, about two or three sessions ago, we did an entire hour on GLP-1 drugs and Alzheimer's. So we're going to give resources at the end, and you can go find an entire hour on that.

DR. BEAU ANCES: I'll jump in on that for one second. The GLP-1s we do think could have early satiety—

NANCY KEACH: Can you explain satiety, please?

DR. BEAU ANCES: I'm so sorry. My bad. So early feeling full, and so that you're not eating as much. And then we also think that the gut microbiome, so those little organisms-- so when we eat something, it's not just us eating. It's millions of these microbes that are in our gut that are also having dinner with us or lunch or breakfast with us. And so those foods are influencing how you feel, and if you feel stuffed or not. And you can just think about this, when you're going to Thanksgiving dinner, and

you're having some of those foods. And you're feeling, oh, I feel really full on this. And I don't want to eat anymore. Well, it's this interaction between those microbes that are then breaking down some of the stuff and particular fiber or other products. And they're releasing these things called short chain fatty acids. Those same kinds of fatty acids are the fatty acids that GLP-1 is doing. And so they're mimicking that kind of effect. And so what you're eating can almost lead to, and we know, can influence how full you feel.

NANCY KEACH: And Sue, who's asking a question about a vegan diet in the chat, we're going to get to that. We will absolutely get to that-- a very commonly asked question.

So let's step back. What's the gut microbiome? Mason, if you want to throw up for two seconds, I took my very first stab at generating an AI-generated image, a metaphor. I asked it for a metaphor. So you'll tell me how well ChatGPT did. So I had it design this healthy gut-brain axis, and we're using the tree as a metaphor, with the roots as the gut, and the leaves and branches as the brain. And then something called dysbiosis. But I thought it was very cool that AI would generate that image. So can you speak to that image and give us a sense. So what does a good gut health look like? What does a healthy gut look like, and how is it affecting the brain?

DR. BEAU ANCES: So great question. So first, let's just go back. As I was mentioning before, you are what you eat. And what we're doing is, we think that the most innovative part of our body is the brain. The second most innovative party is actually our gut. And so there are large connections, and there is even a nerve, a special nerve. It's called the vagus nerve, that talks directly from the brain to the gut. And it feeds back. And you know that because once you're full, and you feel full, or you feel hungry, you are telling your brain, I need to go get something to eat, or I'm full. And I don't need to eat anything more. So there is this constant interaction between the two. Typically, we have these microbes that are then breaking down the different nutrients that we're eating, and they are processing that. And then we take that in as a product. And then we use that sugar, or we use other things that they're taking up. What happens is

that, in certain cases, the microbe could be-- there's this balance between different organisms. And if certain organisms dominate, and other ones don't, they can actually destroy the gut and that lining and then lead to a leaky gut and more inflammation. And that inflammation then can go around the body and even go to the brain, and again, lead to this inflammatory response and connections between the gut and the brain. And so we think that there's this breakdown that's occurring in the gut, that's super important, that's leading to some of these diseases.

NANCY KEACH: And I'm asking this because there were so many questions about what is a leaky gut? So it sounds from what you just said, leaky gut, the lining is breaking down because of the—

DR. BEAU ANCES: Dysbiosis because there are different microbes or organisms or species that are different, that are some that are more dominating and other ones that are becoming less dominant.

NANCY KEACH: And is it because then inflammation results, or is there actually leakage? I think the people want to know about the leaky gut. And someone actually wrote, Darlene from East Wenatchee, Washington, "Is leaky gut just a way for supplement companies to make money?"

DR. BEAU ANCES: So we'll go a little technical, and I apologize for that. And then I will pull back out. So what happens is that there are different things that are released. And one of those things we call is lipopolysaccharide, LPS. And that can be actually very deleterious and can actually stimulate this inflammation. And so what happens is—

NANCY KEACH: Deleterious means bad.

DR. BEAU ANCES: Bad. I'm so sorry, my bad. So it can lead to a breakdown in the gut. And so it does become a little bit leaky, and then there is this inflammation. And then that stimulates a whole process that's going on. And this LPS that is stimulating this inflammation because there's this break, and now it's getting into the bloodstream, is then stimulating a reaction in the body and then can also stimulate something that's in the brain.

NANCY KEACH: Got it. People are writing so many questions already. I'm

going to skip some of the prep because you mentioned the vagus nerve. And Shawn wrote, "Are any of vagus nerve stimulators worth looking into?" I guess specifically for this.

DR. BEAU ANCES: Yeah. So there are studies that are ongoing, that are looking at that. And then in Parkinson's disease, another neurodegenerative disease that many of you may know Michael J. Fox has, and that is these classic signs of a tremor, so this pill rolling tremor, some rigidity, some instability and slowed movement. So that's these classic signs of Parkinson's disease. It's been shown a vagotomy, meaning cutting the nerve of the vagus actually improves symptoms. So we haven't done those kinds of studies, but there are other studies that are going on, that are looking at the role of the vagus nerve. I think it's still early in this kind of situation. I think more people are looking at, as others have commented, supplements, probiotics or prebiotics. And maybe we want to talk about some of those things, as I know a lot of people have a lot of questions about those.

NANCY KEACH: Yes, we definitely had a lot of questions about those, too. Before we go directly to prebiotics and probiotics, I'm going to ask a couple-- because my second category of questions was, first, was like, what is gut microbiome, and then what's the connection? And so in what's the connection, Lynn from Lantana, Florida, wrote a question that made me laugh. She said, which came first, the gut problem or the Alzheimer's? So how do you know, if your brain is affecting your gut, or your gut is affecting your brain?

DR. BEAU ANCES: Yeah, which one is the chicken or the egg? Yeah, I'm with you exactly on that. So maybe I can explain some of our results that we've been looking at and trying to see how early are their gut changes. And so what we have done is, we have taken individuals here at WashU, at the Knight Alzheimer's Disease Research Center, and asked them to do a number of studies. So one is to take pictures of their brain. One is to do something called a lumbar puncture to look at the spinal fluid that's around the brain. And then we've also done some thinking tests, blood tests, and then asked them to take a little hat and do their business. And then we have couriers that take the poop. Yes, this is correct. We have

special couriers that take the poop, and then we have freezers full of poop. Yes, we actually have freezers full of poop. And what we've then done is looked at that poop and try to see what is the composition of that poop. So it's called the microbiome and these taxa or species. It's just the fancy terms of what are the organisms that are in it.

And then we tried to say, we've taken individuals that are cognitively normal, that don't have any of that amyloid or tau. Then, we've taken individuals that have had amyloid and tau, but are still also cognitively normal. We call that preclinical Alzheimer's disease. And I know there have been a number of discussions about that whole term. And then we've looked at symptomatic individuals and tried to see when are those changes happening in the gut microbiome. And what I tell you is it probably is not the earliest change, but it is one of the earlier changes. What do I mean by that? Well, when we looked at those individuals that had amyloid and tau changes, there were already-- In a preclinical, there are already changes in the gut microbiome, meaning that there were some species that were up and others that were down, that were different than those that are the controls or what is seen in the general population. And so that tells us that there are already changes that are occurring. Do I know which one caused which? The only way to do that is repeatedly sample individuals and then see when they change with the amyloid and when do they change with the gut. And that's what we're actually doing right now, longitudinally following those individuals. But it does suggest to us that these changes in the gut are occurring pretty early on, and they pretty much change, and then they stay fixed in this. So there's not as much diversity in the gut. And they stay fixed in a pattern. And they continue to be in that pattern, as people get more and more impaired.

NANCY KEACH: That's so fascinating. So they're changing together, so to speak. We just don't know which one is-- or whether it's a whole systematic change that's just affecting both. We don't know.

DR. BEAU ANCES: We don't know that yet, and that's a great question.

NANCY KEACH: Yeah, and I do want at the end of-- because people got us to the holy grail by asking, are there studies we can participate in, which is, of course, always are, as an organization that funds research, without people participating in clinical studies, we can't learn. So at

the end of the program, I'm going to ask you about any studies that are available. And people are also asking about vagus nerve studies. So that's interesting, too.

I wanted to ask-- Lisa from Tempe, Arizona, "At what stage of the disease can improving the gut microbiome no longer improve health outcomes with Alzheimer's dementia? And I guess I should have asked the question before that, since we're talking about them happening simultaneously. Do you believe-- or does the data show that if you improve your gut microbiome, you can potentially also be improving your brain function?

DR. BEAU ANCES: Great question. And so we're really looking at that right now. And we do certain kinds of tests and certain kinds of therapies for individuals that have inflammatory bowel disorders. So you may have heard that on the TV. Do you have IBD or inflammatory bowel syndrome, IBS, and what's going on in you. And can we give you certain kinds of medications for that? And we even do something that's radical? I know this is going to sound really weird. Can we do something called a fecal transplant? And you're going to say to me, well, what does that mean? What we do is-- and we do this in certain other inflammatory conditions. We actually take the poop of other people, put it into the gut, and now put those microbes to be now dominant and taking over that area, and so those bad ones are diminished and the good ones are there. And so we do something called a fecal transplant. Now, we're not doing that yet. They're doing that in animal studies and doing that in the research side. But we're not there to that kind of level of changing the gut. But you can change the gut by doing certain kinds of things. So what you're eating. And so let's just go into that of these probiotics and prebiotics, just to talk about that. So probiotics are these bacteria that are found in fermented foods. So that means yogurt or buttermilk or other kinds of stuff. Prebiotics are other things, like fiber. And the fiber is really, really important because that nourishes the gut. And it's found in stuff that you may eat, like bananas or garlic or leeks.

And the reason why, as I was saying to you before, is that fiber is really good, and it's certain types of fiber that are really, really good is that it is the great nourishment for those-- it's the best food for those microbes.

And they really like that kind of food. What they don't like or they act differently, is those ultra processed foods that some of us, especially in Western diets, are having. So if the fiber is there, certain microbes can come and become more dominant, and other ones become less. And that gut balance favors the good ones and less of the bad ones. And if there's more of the good ones, then there's less of this inflammation. There's less of this LPS, that I was saying, that's released, and then there's less of this inflammation that's going systemically. And so if you eat other kinds of food, like those ultra processed foods, they don't have a lot of that fiber. And because of that, it's not as good, and they can't break it down. And then it leads to more of an inflammatory condition.

Now, do we know, and is it easy to study all of that and figure out how does that lead to Alzheimer's disease? That's really tough, because we really have to have good dietary intakes and following that. It's hard to capture all of that. And you really have to follow people a very long period of time to figure out all the steps that are in there. But what we are thinking right now is that there are some things that are good, some things that are bad. How can we influence that balance, so there's more weighted to the good microbes and less to the bad ones that are there.

NANCY KEACH: So you talked about fiber, prebiotics, I guess, bananas, garlic, leeks. And then you talked about things like yogurt. And I think Dr. Rossi from BrightFocus Foundation who's answering all of your questions in the chat—without sugar. And we have a lot of questions about prebiotics and probiotics. Let's start, first of all, with, are they all equal? And I'm going to say these so that I don't forget them. A lot of people wrote in how expensive, how they can't-- what are five things that normal people can do who can't afford these ridiculously expensive probiotics and prebiotics? And the third question-- different question I'm going to get to. You mentioned IBD, which several people wrote in about and diverticulitis. And I will say I have had Crohn's disease since I was 12 years old. And so, sometimes, when people say, have a high fiber diet, I can't eat that. So because I have a different illness, I can't necessarily eat the same-- the healthy foods that people recommend, leafy green vegetables. So, sorry, I just threw three different questions.

DR. BEAU ANCES: Let's separate them out. So what are we thinking about, are all fibers the same? And the answer is not exactly. And so there are this resistant starch fibers that seem to be a little bit better for us. Those are found in beans lentils, peas. I talked to you about bananas. Other fruits, I think, apples, pears. And then those whole grains, so when you're eating the breads, the whole grain breads, and even brown rice or other kinds of stuff. So those seem to be a little bit better. Not everybody can tolerate that. I agree with you. And so you have to do it in moderation. And so what I try to tell people is that-- now I am not a dietician, and I'm also going to say that straight out. And I'm not a GI doctor. I'm a simple country neurologist, but I try to think about these kinds of foods and what we're eating.

And so one of them is the ultra processed foods. So let's just go through those. Those are all those cookies and all those sugary cereals. And I'm going to tell you, I eat some of those, some days-- or the pastries or that stuff. And the reason those things are ultra processed is that they are there to have a longer shelf life, meaning that they can be at the stores for a longer period of time. And they get rapidly absorbed, and they confuse, and then they lead to certain microbes. Because you're eating all of this. They will now dominate, and other ones will become less. And so what I would say is, if you can switch to some certain types of foods, like instead of having say, white bread, you do some high fiber versions, like whole wheat bread. If you try to add some fruits or vegetables to your diet. I mean, we're never going to be perfect. And some days, during the holidays, of course, we're going to have some certain stuff, and that's perfectly OK. But if you can add in some of those other nutrients to help with that balance, that could be really, really great.

So let me give you an example, because you also asked about this. Like, say in the morning, you had cereal. So you could either have the super jazzed extra, that my kids love or used to love of the super sugar-coated ones. Or you could say, you know what, I'm going to have a Greek yogurt. I'm going to have something that's got some probiotics in it. And then I'm also going to have some prebiotics. I'm going to have some nuts, or I'm going to have some berries with that. And that may be just as good or

even better for my gut. Same thing with lunch. You could be like, I want to have a big sandwich with all those ultra processed meats and all that. Instead, you could look for other brands that are less of that. Or I have it on white bread. I'm going to have it on whole grain bread or look for ones that have less additives. Or at dinner, you could be, say, I'm going to have some pasta, but I'm going to have it with a whole wheat pasta. Or I'm going to add extra vegetables to the sauce, in my pasta sauce, and doing that kind of stuff. So there are ways to do this that don't cost as much money and may not be in all those supplements that you may be thinking about.

NANCY KEACH: Yeah, and I did want to get to that, about the supplements because as I think Dr. Rossi put in the chat, the supplement market is unregulated. Even a lot of the things you guys see, we all see advertised on TV a ton, there is no scientific data to back them up. And it's pretty much impossible for all of us regular folk to be able to distinguish what's a good probiotic, what's a good probiotic as a supplement. So Dr. Ances, this is the million-dollar question here is, if we're not going to put all our money into buying all of these products that are being marketed to us incessantly, what are-- somebody wrote, what are the five best things you can eat? Or is there-- or is there a probiotic or a prebiotic that you do recommend, as not being full of sugar or not being inert. So I'm putting you on the spot a little bit, but there are questions, like-- Lauren from East Islip, New York, "Hoping you provide examples of keeping the gut healthy and filled with the good stuff."

DR. BEAU ANCES: Yeah, so I don't-- full disclosure, I'm going to say this straight out. I have no stock or equity in any company or anything else. I don't have a single or specific probiotic that I would say this is the one to use and do that. So I don't have a specific recommendation for that. I think some of the stuff that I talk to you guys about before, of changing the diet and doing it a gradual or progressive manner, is what I try to encourage. I mean, I try to encourage more people to have some kinds of probiotics and see if they feel more full from that. Absolutely, do nuts, vegetables, certain kinds of fruits for doing that. Try to encourage people from the high sugary kinds of stuff that maybe they be consuming. So I don't have a one-- like, here's the one thing that if you took this, then it's going to cure all of this.

I'm fine for people having more fiber and other things that are also antioxidants. So that's some of the berries and doing some of that stuff. And I'm also fine-- we talked a little bit, or somebody mentioned about vegan diets. I think they're fine. They're very good. They can really give you more high fiber, some of those antioxidants, and some of those other good things for the thing just need to watch to make sure that you're taking in all of the other vitamins that you would need to have.

But my answer is, there are many different ways. And then we have also seen certain kinds of diets, at least, from the Alzheimer's point of view of stuff for a Mediterranean diet. So some of the cooking that's done with that and some of the oils that are done seem to be somewhat protective in individuals. And so also encouraging that, as well as other healthy lifestyles, so exercising. And I tell people, you don't have to run a marathon or do all that stuff. Simple walking, doing this, and also sleep, which you guys have also talked about before, other ways that can be done all together could be a much more healthier lifestyle.

NANCY KEACH: And I think you hit on what we covered in our last episode with Dr. Laura Baker on the results of the POINTER Study, that you don't have to change everything in your diet all at once. So start by making adjustments that you can really live with and sustain and then increase them. So don't feel like, suddenly, you're never going to touch anything again, and you have to go to a completely different store. But I talk about the book Atomic Habits. Start by changing some of the small things and then continue that. And also, the POINTER Study showed-- I know many of you were on that episode, that doing those things that Dr. Ances just mentioned in combination. And same thing. If you're going to try to exercise more while you're starting to change your diet, you don't need to run the marathon. Start with small things. Walk to somewhere that you would normally drive. And the combination of those things and social interaction and staying socially engaged, watching your blood pressure, all of the things that we discussed, do them little by little, and in combination, they will make an improvement. And now we have the data to prove it.

Dr. Ances, I want to ask, because you started to touch on the vegan

question. Our friend Tom from Carmel, Indiana, wrote, "What do we understand to be the impact of animal-derived foods and proteins, meat, eggs, dairy, on the gut microbiome compared to whole plant-based foods with fiber." So I think it's great. You said, yeah, vegans, OK. Because a lot of people said, is that a problem if I'm vegan? But what's the difference between eating plant-based products rather than a fully—

DR. BEAU ANCES: Yeah, so some people have a Paleolithic diets and have those kinds of things. So some people have weight loss from those. Those can be good. But you need to also be watching your total intake for that. I think the vegan, what it does, is that you do want some of these fiber, and they have diverse plant-based foods in the vegan diets that can really be helpful for individuals. I'm not encouraging everybody to become vegan all of a sudden. But it also makes these other products, one of these things called polyphenols. And these are plant-based that are not based in animal products, that really have a stimulation of certain of those good bacteria, those good microbes, and can lead to significant weighing of that balance that is better for those kinds of organisms. And so they also-- because those organisms are then more stimulated, they are releasing that other thing that I was saying to you guys before, those short chain fatty acids, which we seem to be thinking is a really good factor and can stimulate large areas of the brain and other areas of the body, and that can be very beneficial. And so I don't propose that any one diet is the best diet. I think anything in moderation is more realistic.

NANCY KEACH: And I'm going to point out, Sharyn, Dr. Rossi has put in the chat, I think twice now, a list of a high fiber food list. And we will email that out when we send around a recording of this episode. I want to ask you a lot more questions about this, but since—

DR. BEAU ANCES: Do you want to talk about genetics? Because I know lots of people are talking about—

NANCY KEACH: I do want that. You know what, if you want to skip-- yes, I was going to start talking about testing and so on. But let's talk about genetics.

DR. BEAU ANCES: OK.

NANCY KEACH: Let me ask you a question first, because I want people to know we're reading their questions. And so Karen from Setauket, New York. "Can people with APOE4 genetic risk factor decrease risk with certain pre and probiotics?"

DR. BEAU ANCES: Yeah, so let's break that down and just make sure everybody's on the same page. So apolipoprotein-E is something that we think is the shuttle that helps in lipid metabolism and is very important risk factor for Alzheimer's disease, meaning that if you have one copy of it, you have about a three-fold increased risk. That doesn't mean you will develop Alzheimer's disease. It just means you're at an increased risk. And if you have two copies of it, you have about a 12-fold risk. Again, not everybody that I have, who has APOE4, has Alzheimer's disease, but they are at an increased risk. And so the question is, are there ways that we could compensate with that? And then does APOE4 make a difference in the gut microbiome in looking at that. So we've looked at that in a preliminary study. And the answer is, it doesn't seem to be that much of a difference, at least with gut microbiome. However, there are animal studies, and I can't remember what-- rodent or something-- that has this APOE4. And it did lead to changes in the gut microbiome. So I think that there needs to be more research in this particular area of looking at APOE4. Do you need to change your diet if you're APOE4? I wouldn't say directly no. I think, as you saw in the POINTER or other studies, I think it's a combination of factors that are going to be important. But I don't think that there is a specific APOE4 diet per se for individuals.

NANCY KEACH: Diane from Long Grove, Illinois. "I come from a large family, and most of us have gut issues, and dementia is becoming more common in our older population. Are there studies adding genetics to the mix?" So I guess studies looking at microbiome and Alzheimer's.

DR. BEAU ANCES: Yeah. There is some studies by us and then some studies from Duke and a couple other places that are starting to look at that. You need to have a large enough of a sample to do that. Many of our Alzheimer's Disease Research Centers have a higher predilection, meaning they have a higher percentage of individuals that are APOE4, because they're looking at families or family history and selecting for individuals

for that. That being said, I don't know, off the top of my head, if there's a specific genetic study that's incorporating all of that. When we did an analysis-- I will say it this way-- we took the blood based biomarkers, and we took our PET imaging markers or spinal fluid measures. And then we said, OK, if we took out one of those markers and added the gut microbiome-- so if we used age and a couple other factors, APOE4 status and a couple other things, how good were we predicting? We were good. We weren't as good as just the amyloid alone in predicting in an individual having disease, but we were getting closer to it. So my answer to you is that it's probably multi-dimensional in this. And that if you add on a couple of these factors, plus a couple other things, you get to a good predictive value in identifying individuals. But I think it's a combination, not one specific factor alone.

NANCY KEACH: Thank you. I'm just going to hop back to something because I know a lot of people have asked about this. But I want to go to Michelle's question in the chat. "I've heard that taking pre and probiotics in supplement form is wasteful because most are excreted before being fully absorbed or utilized." Is that correct? So I know I'm backtracking.

DR. BEAU ANCES: No, it's fine. It's a great question. So some of the supplements that you take will just be-- if you are already high in it, and/or if you have not the best of gut microbiomes, it may not be totally absorbed. So I think do the probiotics help? They're pretty easy to take. They're not overly expensive. Simple things like yogurts, as we were talking about or other things that are probiotics, are relatively easy. Are you absorbing all of it? No, you're not absorbing all of it. If you start doing this, and then have more and more, then you are going to change the milieu, that balance of stuff, and then they will be absorbed more and more. So when you're first taking it, if your system is already out of kilter, it may take some time before the system gets more normal, and then starts to change to the pro side that will occur. So I would say to you, don't expect a result immediately. And I tell this to all my patients, if you're going to make a change, make one thing at a time, give it a little period of time before you move and add on the next thing. Because if you throw on three different things, and you see a change, is it due to your exercise? Is it due to your diet? Is it due to something else? So take things

in moderation. And I try to accentuate, do it one step at a time.

NANCY KEACH: And I always think it's important, too, what you were saying, you're not going to eat a bowl of blueberries, and suddenly, everything will have changed. It has to be over time. And we talked about this last time, that it has to really be incorporated into your lifestyle, not something you make an appointment with yourself to do. So if you can slowly make it your lifestyle, that's going to be the most effective strategy.

I want to make sure we cover this testing and clinical guidance. So Clifford from Baltimore wrote, "What does a microbiome analysis cost? Does Blue Cross Blue Shield Medicare pay for it? And does your physician need to order it?" And so we had several questions about microbiome testing. Stacy from Bethesda-- "Is there a reliable way to test and evaluate the quality of an individual's gut biome?" And I'll ask one more. By the way, it was really interesting to get many more questions from doctors than we normally get. And so here's one from a doctor. "As a doctor, to what kind of lab or specialist should I send my patients for a gut biome analysis? Am I right to think that this is required to create strategic intervention rather than recommending generic pre or probiotics?" And also, I just want to say, even-- so, it's not just us. It's even our doctors don't know the answers to these questions that we're getting from Dr. Ances.

DR. BEAU ANCES: Yeah, so I think we're all still learning on this whole process. So let's just break it down. First of all, what is incorporated in those kinds of testing? And then I don't know of that many commercial entities that are doing the gut microbiome. And I don't think that we usually use the standard something called a CLIA approved, meaning that they're very high specificity, and they run the test. And they're very reliable in running the tests, and they repeatedly see that. I don't know of groups that are out there yet, that are fully at that level for doing that. If you are thinking about this, I usually recommend individuals also to see their GI physician, so their gastroenterologist. So he or she is the person who is often doing this. And it's a tag team combination. And I also tell them to talk to a nutritionist. And I really say, here are all the things that you could be thinking about. It's not just me. And if you're going to do this, if you're having inflammatory bowel disorders, if you're having Crohn's, if you're

having other kinds of conditions, what would be the best diet? And how to talk to a nutritionist and say, what are things that would be good? Can we get these kinds of tests and do that? We don't know yet what are the best ones for Alzheimer's disease and which are the ones that are the worst ones. We're still learning that. That's why we're doing the research, and we're doing the studies right now. We're still in an early infancy in this field. But I bet, in the next couple of years, we'll be able to have those kinds of tests that are going to be available. And if I take these kinds of probiotics, it'll boost up my butyrate, and it'll boost up these other ones, and take down these other ones. And will that make a difference? And how long do you do that for? We're not there yet, but again, I think that's where the future is going to be moving towards.

NANCY KEACH: And you just mentioned butyrate, and somebody asked a question about that, and I had to look it up. So will you tell everybody what is a butyrate?

DR. BEAU ANCES: All right, so it's a byproduct that's released, that helps in certain kinds of pathways for senescence, meaning cell life and for slowing down an aging process. And so it's one of those factors that we think could be important. What is the exact role? We don't know, or I don't know as much about that. I would have to refer to others.

NANCY KEACH: That's interesting because two people tried to explain it a little bit in the chat, and their answers are also different than the one Dr. Google gave me.

DR. BEAU ANCES: I think we're still learning.

NANCY KEACH: OK, we're still learning. I want to ask-- before I get to clinical trials and future research and so on, I just want to ask one of the patient and caregiver support questions because, let's be honest, it's sometimes difficult to get our loved one to eat in a certain way. And so, Nancy, not me, but someone named Nancy said, "Suggestions for getting your spouse to eat better? His short-term memory is fading." So if we're a caregiver of a loved one, and I know that Alzheimer's does cause sweet cravings. I used to see it with Glen Campbell when we were shooting a movie about him. He would have several pieces of chocolate cake

after-- actually, for his meal. So how would you get him to eat better? Or honestly, at that point, if somebody is past a certain stage, do we just say, eat what you want to eat.

DR. BEAU ANCES: That's a really good question. And let's just go back to why we're worried about eating and doing that. One of the things is that we have-- and there's a lot of literature out there-- is that when people are losing weight, that is a very telltale sign that things are progressing, specifically with Alzheimer's disease. And the reason you can think about it very easily is that individuals are forgetting to eat. They don't remember, did I eat, or what did I eat, or what do I need to eat and doing that. And so you have to build, and you have to pick your battles with individuals.

What I try to tell families is that, if there's a loss of weight, that is a concerning sign for me that they're not eating well. I'm very worried. And I'm worried also about muscle mass and breakdowns and not enough nutrients. Because when you are having Alzheimer's disease, you are having a constant battle. It's a constant fight, and you need good nutrients to help you in that battle to fight this evil, evil, evil disease. And so I encourage people to do certain kinds of supplements. I even encourage people to get something like Ensure or other things, because that's easier to swallow, easier to do. So I tell people, you may need to puree. You may need to thicken stuff. You may need to figure out different combinations of foods that are the best for that individual so that they can still enjoy and do this and still enjoy things that they want to do.

You're right, as the disease advances further and further, I pick my battles of trying to say, well, if they want to have some ice cream, sure, you can have some ice cream. I'm not going to-- but can we get other things as well in so that we make sure that they can have enough strength? They can do enough of the walking. They can be active to a degree, and that we're not having other breakdowns that are occurring. So I moderate it. And some days, you're going to win. Some days, you're going to lose. And you're going to say, this is not one I'm going to-- this is not a hill I'm going to fight for today. But if you can encourage them-- and I think it's important for the individual that was being brought up that has-- if they're having mild cognitive changes, start the diet now, or start it very

early. Because if you can get it into a routine, where they're always taking this, and they're more accustomed to it, then they're going to do that. If you start switching things around on people, especially those that have Alzheimer's disease, they're going to get a lot more confused. They're not going to understand what to do or why this is important. But if they're already in a regimen and a routine, and you have that down, then it's just like, oh, well, we always had breakfast with yogurt. We always had these kinds of things. This is your natural breakfast. Here you go. Here's the bananas. Here's something. You may not have the whole banana. You may have slices of the banana, but you're doing that.

NANCY KEACH: And real quickly before we leave testing and get to research and trials, because I'm not sure if we really addressed it, unless there's a specific reason to have your microbiome test, is there a reason to get a stool sample and look at that, or is it really a reason for a test at this?

DR. BEAU ANCES: I wouldn't do it right now. I don't think we're at that level. As somebody who's doing some of the research in this area, I don't think we're there yet. And I'm being completely honest with you here. I think this is an area where we're learning a lot more. We don't know what are the right things to upregulate or downregulate. I don't know how I would use the stool sample directly for changing what I would do, like, oh, well, if you had these certain things, then you need these kinds of probiotics versus these kinds of probiotics. So I don't think we're there yet. I just don't think we're there yet, nor do we know yet what that is. But I think there are certain things that we've been talking about through this session of a healthy diet, of certain kinds of things that you could do, irregardless. That could be beneficial. But I wouldn't go for a whole gut microbiome testing and then say, I'm going to change my whole thing yet based off of this, because we just don't have enough information yet.

NANCY KEACH: So Diane from Cos Cob, Connecticut. "My gut has been a mess for four years. How do I get involved with the study?" Now, I guess there's studies when your gut is a mess, but how can we get-- I know about those. But are there studies that people can participate in, looking at the connection between the gut microbiome and dementias, Alzheimer's, or other neurodegenerative diseases? And if you can't, list

them now. Because we do a sub series on clinical trials, where we'll take one trial, and we'll just go deep into that trial, and how do you participate. And we always look for ones that have sites all over the country so that it's not like you just have to be in Tampa. But are there studies that people can participate in? And if you tell us that there are, we can also send out some information in our post-episode emails.

DR. BEAU ANCES: Yeah, so there are some-- so how the landscape is right now is that there are some Alzheimer's Disease Research Centers, and they are sprinkled throughout the United States. And they are in almost every state, but not every. So I don't know of ones in Montana or Alaska or some other places, but they're in many of the places throughout the United States. And you may want to go to that local Alzheimer's Disease Research Center and ask them if they're in or participating in collecting the gut microbiome. There would be no intervention, meaning that we wouldn't be giving you certain medications. We're not there yet for a clinical trial, that I know of, that's going on through these centers to do that. However, some of them are participating and sending those samples to a couple places, where they're getting analyzed. And you can be important for us to understand this. Because the only way we're going to learn is from people who are willing to be research volunteers for this. And I can't tell you how important and how much it is important we give back to our participants in doing that and thank them for doing this kinds of stuff, because this is really advancing the field. I don't know of a single study that was out there. There was a study that was using something from China, from seaweed, but that quickly failed and is not out there and would not be recommended at this time.

There is not a single study that I know of specifically, but you may want to talk to your centers. And then if you're having certain kinds of intestinal issues, they may be related to Alzheimer's disease, but they may not be at all related to Alzheimer's disease. And I would strongly suggest that you see your primary care physician, and he or she then may be referring you to a gastroenterologist. So that's a GI doctor, that he or she could do further evaluations. Some of those are simple tests of swallowing stuff to see how the coating of stuff is, and how the stomach and how the intestines look to more complicated, where they do little biopsies

of particular areas to other kinds of things, where they then need to consider other kinds of treatments for that. The one other thing that I would strongly recommend to people-- and we need to take them, but I think some people are overtaking them-- is antibiotics. And I just want to make sure that people understand. If it's needed in doing that, that's very important. But those antibiotics also wipe out the gut flora and make someone's be more dominant than others. And so when we're doing our studies, we actually ask everybody if they're on antibiotics and what are those antibiotics. And we have, sometimes, over prescribed on these antibiotics. If you have a cold and you take this antibiotic, and you're doing that, when we really don't need to be doing that. And that can really affect the gut flora. And so watching out for that and trying to think about those, as well as other medications and deprescribing on certain medications, are simple things that you can also be considering.

NANCY KEACH: Thank you so much. There were a lot of questions about antibiotics and so thank you for getting to that. I'm over time for which I apologize to folks. I want to just call out Sean in the chat, who says, "I'm in for anything. I'm in Western Massachusetts." There's some great Alzheimer's disease research centers in Massachusetts, up at Harvard, at BU. So you have a lot of choices, Sean. Go for it. Please participate. You also tend to get really good care when you participate in the clinical trials. So I always do try to recommend it.

I want to thank Dr. Sharyn Rossi from BrightFocus Foundation, who's director of Alzheimer's Research Portfolio, and has been answering your great questions in the chat. Thank you for-- and I want to thank Amanda Russell and Alexa Villarreal from BrightFocus also, our producers, and the team at M Squared, who provides this platform.

And I will tell you that the reason-- I don't know if you're all seeing it the same way I am, but the reason why I don't just put the speaker view up is because I like to see all of your faces, and when you're writing down and taking notes. And it's just very helpful to me because BrightFocus wants to really be connected to you and your questions, and without seeing you, that's hard. Even though, as Dr. Ances said, most of us have things going on in our own lives. My mother has MCI and is 95. Most of the research

people, when you get-- I'm going off here. But when you get skeptical about pharma, just know that most of the people I know in pharma have family members with Alzheimer's and are as passionate about trying to find something that really works as all of us. Maybe more so because they feel an obligation to do something. So, thank you, Dr. Ances. We're going to try to get you back here because there's so many questions. So please come back.

If you all have questions, and I know that you do, that were not answered today, this is a list of previous episodes. So you can see in August was the GLP-1 analog session with Dr. Paul Edison from Imperial College London. Dr. Laura Baker on the US POINTER Study has a lot of practical suggestions that you can do today. These are all available for free on our website at brightfocus.org/zoomin and on YouTube, on the BrightFocus channel on YouTube. So please take advantage of them. It's our great joy to provide these to you.

We have other resources available for free. If you want to request copies of any of these pamphlets, you can call 855-345-6237. Or you can just email, reply@brightfocus.org And we will get back to you. We are getting your messages and your emails. We will be sending out a recording, as I've mentioned several times.

And this is really important to me. If there's somebody that you know, that this program would be helpful to--please share this link, brightfocus.org/zoomin, and invite others to attend. This is how we get the word out. And we really, really want to get all of this incredible information that we have from researchers into your brains, and not just in the labs.

On Thursday, November 20, I have a wonderful guest, who's coming back for the second time, Dr. Marwan Sabbagh. He is brilliant. And he's going to be talking about the oral drug, blarcamesine, that's being tested now, and other oral therapeutics, meaning drugs you can take by mouth that are being tested for Alzheimer's disease now that are in trials. So I highly encourage you to take advantage of that.

I want to say, as I do each episode, life is so short. Tell everybody that you love-- that you love them. Hug them. Hold them close to you. Thanks

again to all who joined us. I hope you have a great Halloween with the grandkids and the kids. And do write to us. We really want to hear from you. Until the next time. Thank you again. Thank you for attending and have a great couple of weeks. Until we see you again. Take care.

Resources:

- List of fiber foods to add to diet from Mayo Clinic: https://www.mayoclinic.org/healthy-lifestyle/nutrition-and-healthy-eating/in-depth/high-fiber-foods/art-20050948
- Article: How GLP-1s Could Transform Alzheimer's Treatment
- Previous Zoom In episodes mentioned:
  - U.S. POINTER Study Update: Lifestyle Program Significantly Improves Cognition in Older Adults
  - Can GLP-1 Weight Loss Drugs Treat Alzheimer's?