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

How Is Alzheimer's Disease Diagnosed? From Pencil & Paper to Eye Scans & Blood Tests and Everything In Between
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Transcript of Zoom with Randall J. Bateman, MD, Charles F. and Joanne Knight Distinguished Professor of Neurology and Director, Dominantly Inherited Alzheimer's Network (DIAN) and the DIAN Trials Unit (DIAN-TU) at Washington University School of Medicine in St. Louis

Please note: This transcript has been edited for clarity and brevity.

NANCY LYNN: Good morning. Good afternoon, everyone. I'm Nancy Lynn. Thank you for joining and for joining again. I see people are still coming in. We had over 400 registrants for this, and over 100 questions pre-submitted. I'm going to jump right in because we have a lot to get to and we have an Alzheimer's star with us today. I'm just absolutely delighted to introduce Dr. Randall Bateman, who is the Charles F. and Joanne Knight Distinguished Professor of Neurology at Washington University School of Medicine in St. Louis. Dr. Bateman is also a scientific co-founder and board member of C2N Diagnostics, the company developing and commercializing novel diagnostics. Specifically, the Precivity blood tests for Alzheimer's and related forms of neurodegeneration to improve treatment decisions and patients' lives. Also, very happy to say that Dr. Bateman has received several research grants from BrightFocus Foundation. And if you can go to the next slide. The first, there we are,

was in 2008, and I couldn't resist Dr. Bateman, showing that first grant application from 2008, which he was awarded. And I will call out that this is what BrightFocus does, is fund researchers early in their career and continue to fund them until they give us breakthroughs like blood tests. So this was when he was an emerging scientist. I think he has arrived. Welcome, Dr. Bateman. And let's go right to the next slide. I wanted to start with this question. Why is early detection and diagnosis of Alzheimer's so important?

DR. RANDY BATEMAN: Well, good morning, or good afternoon, or good evening, depending on where folks are calling from. Thanks for joining. It's a real pleasure for me to be here. And before I start in with the questions and addressing them, I just want to comment that BrightFocus has been an incredible advocate and supporter of being right at the very cutting edge scientific advancements. And it's those scientific advancements that have led to the ability to diagnose Alzheimer's disease at a precision, at a way that we can never do it before. And the world is completely different today than what it was even just a year or 2 years ago. So much 5 or 10 years ago. So I'll try to answer this question by putting it in a bit of perspective. When I started...by the way, I was surprised to see my photo when I was younger. I'm sure that photo was pre 2008, though I was quite a bit younger in that photo. But back when I trained, 25 years ago in medical school and residency, we were taught, all students and all doctors were taught, that in order to diagnose Alzheimer's disease someone would have to die, pass away, and then you would have to do an autopsy on their brain to determine if they had amyloid plaques and tau tangles to figure out whether they had Alzheimer's disease in life. So, it's a diagnosis that could not be made during life. And that's a really tough thing to do, because what that means is when you see patients, you can't diagnose people while you're seeing them. And that is incredibly limiting. And so, the scientific field is really focused on how do we detect Alzheimer's disease and how do we diagnose it while people are still alive? And over the years, you know, over the past 25 years has been phenomenal progress.

And what I'd like to emphasize is that the ability to diagnose Alzheimer's disease today with a single blood sample, a blood test, that's as accurate as our neuropathological diagnosis or PET scans or cerebral spinal tap

tests is really phenomenal. And it's really changing everything that we do from how we diagnose people in the clinic, to how we treat them, to, how we run clinical trials, to how fast we can develop new treatments. And so the question, "Why is it important to detect Alzheimer's disease and other dementias as early as possible?", the answer, it turns out, is the same for almost all diseases in medicine. If we can detect a disease early in its stage and treat it and manage it then, it's almost universally better than waiting until the disease gets more advanced. And so imagine I mean, we all know this right? So we all go in and we get our cholesterol and our blood pressure checked to try to prevent heart attacks and strokes at the earliest stage possible. We do cancer screening and cancer preventions long before people get cancer trying to prevent them from getting cancer. And the field is now moving to where we may be able to identify people who are at risk of getting the symptoms of Alzheimer's disease, but we could treat them and prevent them from getting dementia, memory loss, and the progression of Alzheimer's. And many of us think this is where the real large impact and turning the tidal wave of Alzheimer's disease, turning it back. We've been successful in this with cardiovascular disease, with heart attacks and strokes. We've been successful in cancer. Numbers of people dying from cancer is actually decreasing. And I predict that within the next 5 to 10 years we'll become successful in preventing Alzheimer's disease. And so, one thing that's critical for that, though, is, we have to know who's at risk for getting Alzheimer's disease in order to treat them and prevent them. And today, something that's different than last year at this time is in the clinic today we are now removing amyloid plaques out of patients with Alzheimer's disease at a very early stage. And so we need an accurate diagnosis to know who to treat and who's eligible for that treatment. So there's more reasons than ever, and more hope than ever for why we need early detection. And the wonderful thing about it is that at this time that we have interventions that are having an impact on the disease. We also have in hand diagnostic tests that can say with high accuracy whether someone has Alzheimer's disease or not.

NANCY LYNN: And thank you so much, and you can go to the next slide. I think it's also worth reminding everybody that, and tell me if I'm saying this correctly, that the pathological changes related to Alzheimer's

disease and other dementia can begin as early as 10 to 20 years before symptoms are actually occurring that can be observed. So is another reason there that the earlier you're getting treatment the likelier you are going to be able to reduce your risk.

DR. RANDY BATEMAN: Nancy, that's absolutely correct. And let me expand on that just a bit. So we've learned over the past 10 to 20 years that there's a silent period to Alzheimer's disease. The amyloid plaques begin building up just as you said, 10 to 20 years before the first memory loss, the first symptoms of Alzheimer's disease set in. And so one could look at that and say, well, that's kind of scary, you know, the plaques are growing in the brain silently, and the person doesn't know it. But it's actually a window of opportunity. It means that there's time, there's actually a good amount of time to intervene. And these tests can, some of these tests can identify these amyloid plaques as they're growing before people get symptomatic. And by identifying the people who have these plaques growing, we know that some 80 to 90% of those people, if they live long enough, they will get Alzheimer's disease symptoms, that it gives us a window of opportunity to use these early diagnostic tests to identify who's getting the plaques and then to do something about it.

And so we have all the pieces here. We now have the knowledge of when Alzheimer's disease begins, and how it starts in people. We have the tools to detect the Alzheimer's process, including amyloid plaques. And we just now have treatments that can reverse and remove these plaques out of the brain. And so what's happening now is there are clinical trials where these are being put together, the knowledge that it starts in a silent period 10 to 20 years before, the screening test to identify who has those plaques building up, and using these drugs to remove the amyloid plaques before people have memory loss. That's happening right now in prevention trials. So I lead a large global network of centers that is running prevention trials for people who carry mutations, where we know they're going to get Alzheimer's disease at a very young age, thirties, forties, and fifties. But there are also trials for just the average person who's old enough, over the age of 50 or 55, where they can be screened with these blood tests. And this is happening today to determine if they have plaques, and if they do have plaques, they get enrolled into a trial to see if they're treated with

a drug to remove those plaques, can the onset of Alzheimer's disease be prevented? And I think that's incredibly exciting. In the next few years as these results come out, it'll tell us a lot about that.

NANCY LYNN: And I put this slide together last night, I grabbed an old quote from an NIA article, and I think what you're telling us is that this is maybe not true anymore or not as true. That a lot of the new technologies which we're going to discuss today, and ways of detecting Alzheimer's were only available sort of if you were part of a study and not in a regular doctor's office. So I'm going to let you address this. Where are the tests now available? And who do you see to get them? And of course we have people who are in rural areas. Somebody wrote and said, "what do I do if I'm in what rural western Colorado and I want to participate in a trial?" So if you can sort of cover what are the steps to take to try to take advantage of some of these?

DR. RANDY BATEMAN: Sure, sure. So this statement was more accurate when it was printed, and it says 2020 to 2021. And so just a few years ago it wasn't commonly available that they had these clinical tests available in the doctor's office. Well, most of the tests we were using were for research. But today, that's different. So things have changed. And what, as I mentioned, one of the things that changed, we now have FDA approved drugs that we're using to treat our patients who have early stages of the symptoms of Alzheimer's. So they're not...it's not a prevention trial, they already have symptoms. And we're using these drugs to remove the amyloid plaques. And for that, so I'm a neurologist, and I have a clinic here and there are many doctors here that have clinics, for specialty clinics, for memory loss. Ours is called the Memory Diagnostic Center. And there are centers at most major academic medical centers where they specialize in dementia, Alzheimer's disease, memory loss. So a person can look up their local medical center to see if one of those clinics is there. There are also other ways to find these clinics. You can write, for example, the Alzheimer's Association. You can go online and search for other registries where they can give you information about clinical access. And so right now, the people who are doing most of the diagnosis are specialists. So neurologists, geriatricians, psychiatrists, geriatric psychiatrists, for example. Centers for the Alzheimer's Disease Research Centers oftentimes

have many of these physicians there. There are also primary care physicians. But right now the primary care physicians, I think very few are doing any diagnosis because it's so new right now. It's typically the specialists that have the most experience that are doing the testing.

And so we can now use these tests. And there are three clinical kinds of tests that we can use to help diagnose people and those clinical tests that we have access to, and by clinical tests I mean things you can use in the clinic when the patient comes to see the doctor, things that the doctor and the patient have access to. So there are three classes. One is an imaging scan called a PET scan and it uses a radioactive tracer to go into the brain and bind to these plaques, and you can detect it by detecting the tracers staying longer at the brain.

The second way to do it is to do a spinal tap. And so the PET scans are FDA approved, and the spinal tap tests are now FDA approved. And you can do a spinal tap and take the cerebral spinal fluid and send it off to a lab, and they can run looking for two proteins. One's amyloid beta that makes up those plaques and the others forms of tau. And tau is related to the plaques and the tangles, and how that how those two cause each other. By measuring those two, we get a good estimate of how much amyloid plaques someone has, and what is the likelihood that that their symptoms are due to Alzheimer's disease. And those have been around for a while, but they really haven't been supported in the clinic because they weren't paid for, they could be invasive or expensive. And so there were challenges with that. I think that's really changing. Now, with the advent of drugs that remove these amyloid plaques becoming available. Those are now FDA approved, and there's more coming. So it's a very exciting time.

The latest way to diagnose Alzheimer's disease is by using blood tests. So you can take a sample of blood and measure very much the same kind of proteins that are in the cerebral spinal fluid, but you can measure them in blood and determine whether there's likely to be amyloid plaques present in the brain. And so those are the three main ways right now that it's done, and I would say that we used to rarely use these tests even a few years ago, because they weren't covered or paid for. Now that we have drugs that we need to administer and monitor, there's much greater support for doing this diagnostic testing. And many of us, including our clinic, is

now doing diagnostic testing on large numbers of people and patients. So I think it's available now at specialty clinics. And what I expect will happen is in the future, these tests will become more ubiquitous, more available, and other physicians can use them to help with the hundreds of thousands to millions of people who are potentially affected by this disease.

NANCY LYNN: Yeah, I'm going to stick for a second to the blood rather than to the first question about Dale Bredesen's protocol. I said I wanted to, I think you didn't hear me, but I said I wanted to stick to blood for a second because we got a lot of questions about blood tests And one of them, Dawn just put in the chat, "How accurate are the blood tests?" And there was another question related to that, "Can Alzheimer's now be detected just with the blood? Or do you need the blood and a scan tests to get a diagnosis, to get an official diagnosis?"

DR. RANDY BATEMAN: So those two questions are actually related to each other, because the accuracy of the test tells us how we can use it. And if a test is accurate, let's say you have a test...so how are accurate are blood tests? Well, the answer is, it completely depends on the blood test and how it's being used. So blood test accuracy ranges from about 60% all the way up to 95%. And that's a huge range, right? If you're getting a diagnosis, if you're trying to determine whether you have amyloid plaques, and someone runs a test, and they say, well, this test is accurate, you know, 70% of the time. But 30% of the time it's wrong. You'd say, well, how sure can I be that kind of test is something I want to make a decision on? Like should I take a drug, or how secure is the diagnosis? So that's not a very accurate test. However, if the test is 95% accurate, that's as accurate as our PET scans and our cerebral spinal fluid tests are. And so it can be as good as our best test in other ways. And so in that case, a test that's that good, then what you could do, is you could say, well, I can run just the blood test and if it's really 95% accurate, as good as PET scan or CSF, there's usually not a reason that you have to then follow up and do a PET scan or CSF. But let's say you're in between there and you have a test that's say 80% accurate. Then that kind of test we use is what's called a screening test. So we could say, well, you know, it's 80% accurate you probably have or don't have amyloid plaques, but we can use it to increase

the sensitivity, to say, well, we'll catch, like you know, 9 out of 10 people are positive, but we want to confirm that with a second test. And so the second test might be a PET scan or spinal tab, or even another blood test. So you can use these tests in different ways. You can mix and match them in different ways. And the field is we're figuring this out now based on the properties of the test, how to use them and how to implement them. But one very important question to have the answer to is, whatever test you're taking how accurate is it? It turns out that no test is perfect. There is no perfect medical test. And so you and your doctor should always know, what is this test really telling us? How sure can we be in the results of this test? What does it mean? And these are things that is best discussed with your doctor.

NANCY LYNN: So Beth wrote in. If you had to pick, if you had to pick 2 tests in concert to interpret and make a diagnosis. What would they be, for example, neuropsychological testing and amyloid PET scan? Can you say what two tests you would take if it was your test?

DR. RANDY BATEMAN: Yeah interesting. It's not, I'm afraid it's not so simple. So if there was one, if there was one, it'd be like walking into a clothes store and saying alright, what 2 pieces of clothes should I buy? And you know, of course, there's lots. Well, what do you want to use it for, and what size are you? And there's lots of factors there. What style do you like? With testing, it's not, there's not a simple, straightforward answer to that question. The reason is, it all depends. So but let me give you a common scenario that we're doing now and then try to answer it in a different way. So now, as I mentioned for a lot of our patients, what we're trying to do is we're trying to figure out would they likely benefit from being treated with one of these new drugs that removes the amyloid plaques? And in order to know that, there's many different things we have to know about the patient. And it turns out it's not just two. We need much more than that. So first of all we have to say, well, are they in a stage of disease where we have evidence that the drug could help them? It turns out these drugs work, they seem to work best at the earlier stage, or even the earliest symptomatic stage of Alzheimer's disease. So if they're too advanced, they have less and less benefit, and to the point where there is no benefit. So that's where cognitive tests, clinical assessments, like the clinical dementia rating scale, seeing a patient rating them on the MMSE

or a MoCA scan. These are all clinical tests that we use to figure out how effective they are.

NANCY LYNN: Sorry, when you say clinical tests, you are talking about in the office, this is what we called a pencil and paper test?

DR. RANDY BATEMAN: Yes, exactly. Pencil and paper test. You sit down, and well, now we have them on computer, digital pads and iPads and things. But yes, you're sitting down, and someone is testing your thinking and your memory and the patient's, you know, performance on these things to get an estimate of how impacted that person is. So that's one kind of test we do. The other kind is a clinical tests where we determine what stage of the symptoms is someone in by their family member and by their report? So is the person independent? Can they take care of themselves? Do they need someone around most of the day? Or are they fully dependent on other people to do things for them? So that's a different kind of test that we get in the clinic.

So there's a few other things and in terms of the diagnostic testing, then we want to know, well does the person have amyloid plaques that are similar to the kinds of amyloid plaques that were tested with these drugs. Meaning the amount and the characterization of them. Now that we can get from our PET scans or CSF tests and our blood tests. And, as I said, some of these, and for that question are interchangeable, right? We can do a CSF or a PET or a blood test. But we have to look at the accuracies of them and use them in a way that we have high confidence that that person does or does not have amyloid plaques. So that's kind of a separate question whether you use one of those, or two of those depends on that accuracy. And I talked about that earlier.

NANCY LYNN: Gotcha. And Steve wrote in the questions, "How do you know if your blood test is 60% accurate or 95% accurate?" Or is that why you have these other...would you know?

DR. RANDY BATEMAN: Yes, you should know. So the test before we offer them clinically should have a reported measurement of how they perform. And all these, so we do research on these tests a lot. So, for example, the test I'm most familiar with is the one that we developed here

at the University, and it's been licensed to C2N Diagnostics, which I was a co-founder in that company. And so obviously, I have an interest in the company. But just to point out that at the university level, when we use these tests, we learn how accurate they are. And almost all groups do this right? So when you develop a new test, you want to know, is it 60%, 80%, 95% accurate? And what you do is you do research studies, you determine the accuracy, and you publish that in the scientific literature. And it undergoes peer review, and people look at it, and you submit the data to people to consider. And it's through that process that you really know the performance of the test. And so you do research studies. And so by these research studies, we know now when these researcher studies are published, then then all medical professionals or scientists, others can look. And you could look it up yourself right? You could go to PubMed, or AlzForum and you could look up how a test is doing in terms of its performance. You could ask your doctor what is the performance of this test? And we use numbers like accuracy is one general measure. There's lots of other ways to think about tests. There's terms like sensitivity, specificity, negative predictive value, positive predictive value. For most patients, we don't get into those, their details, but they are important details. But we do get into how we use the test.

But I don't want to stop there because there's a lot more to it than that, right? So it's not just the diagnostic test and the paper pencil test and the cognitive and clinical exam in the doctor's office. We have to know about risk of side effects, and so there's another kind of test for APOE. And there's several ways you can measure APOE now. And so that someone's APOE status, we all have two versions, two copies of APOE, in all of us. And there's an average version called APOE 3, there's a protective version called APOE 2, and there's a high risk version called APOE 4. So think about like that: 2 good, 3 average, 4 bad. And so you can have 2-2, and you'd be highly protected against Alzheimer's. You could be 4-4 and be very high risk for Alzheimer's. But it turns out that depending on what version you are, 2-3, 3-4, 3-3, changes your risk of a side effect of a medication. So now we have test for side effects, and the side effect is called ARIA. And it's these drugs, when we remove the plaques, can cause swelling or even bleeding in parts of the brain. And in most people they don't even notice it. They don't have the symptoms of it. But in very rarely

about 1% or less of the time. People can have a severe reaction to this. So we really need another safety. So we'll get that test in terms of doing this. So I hope this helps answer the question that there's not just, you know, there's not just pick two, and we're done. It really depends on the person and what we're doing. If we're trying to remove amyloid plaques, or we're trying to get an accurate diagnosis, or we're trying to understand future risk of Alzheimer's disease, or relative risk in the family. There's really a number of different tests we can use.

NANCY LYNN: And I'm glad you brought up that the blood tests can detect the APOE status, which is a genetic indicator. My understanding is often for an indicator of early onset Alzheimer's, which may be your fifty-sixties rather than the typical age of onset in the seventies. But I'm going to stand up for Robert and others who have complained to me over the past four episodes that we always talk about APOE but we don't talk about P-tau 181 and 242. So since I did receive a few questions about that, can you explain for all of us, there are now different blood tests or tests that will detect different proteins or genetic indicators within the blood. And these, and I know that there are many, but the ones that are most known, I think, in the public range are the APOE and then these tau tests. So I've had a couple questions about that and what does it mean? And one, in fact, let me just say that is a positive P-tau 181 sufficient to allow entry into a donanemab trial. And if so, how come these other protein indicators are not talked about more or known about more, or known about more?

DR. RANDY BATEMAN: I think I think there's a minor correction there. And for some of you this may sound like a lot of numbers and letters soup. There's a lot to this. And so I have a lab, and there's like 25 people, scientists and PhDs, and all kinds of people who work all the time on figuring out exactly the individual atoms that make up these proteins. We're literally counting individual atoms inside these proteins to measure these things like P-tau 217 and 181, and 231 and 205. And you're going to hear all these numbers. And so I'm going to try to simplify it, because I don't think it's you know, it's I don't want to give you a crash course and biochemistry of Alzheimer's proteins. But I want to try to kind of convey the message.

Alzheimer's disease, this is my understanding of it, really begins when this this sticky protein that exists in all of our brains, it's called amyloid beta, when that amyloid beta begins to clump together and aggregate and grow like a crystal into a plaque in the brain. I think that's one of the earliest changes in Alzheimer's disease. As soon as that begins to happen, your brain is not going to sit by and just let this this foreign thing kind of grow. Because as it grows, it's pulling apart neurons, it's separating what neuron...neurons are the thinking cells, the communicating cells of the brain. They have little synapses where the one sends a signal to the next one, and does all the magical thinking that you do. And so, as this plaque grows, it's pushing apart these neurons, the connections are being torn apart, and your brain doesn't like that. So it tries to adapt. It tries to grow around this amyloid beta plaque. One of the ways it does it, is it seems to rev up its engines to get to get the little synapses, the axons, the fine structures, to grow better around this plaque. Now keep in mind this plaque continues to grow over time. It slowly grows over years.

So as your brain adapts, what it's doing it, it increases the metabolism around here, and it does that, one of the ways that we've learned is that it increases the production of tau, and the tau protein makes up the second pathology of Alzheimer's called tangles. And so tau goes up. So we talked about these biomarkers in the blood, the cerebral spinal fluid, and yeah, we also have tau aggregation PET scans. But there's these soluble forms of tau and they get phosphorylated and phosphorylated is one of the ways that it kind of ramps up the ability to get tau to do things. And so now, all of a sudden, it's phosphorylating 217, 231, 181. And it's doing all this as these amyloid plaques are growing. So in the CSF and in the blood, when you look, what do you find? Well you find more phospho-tau 217, 181 and 231 as the plaques are growing. And what's interesting is, if you take a look, the amount of phosphorylation at those sites, the amount of your neurons are modifying your tau to adapt to it, the more plaques you have, the more phospho-tau you have. So as the plaques grow, the phospho-tau goes up and up and up and up and up. Until finally, it's something changes in the brain, and it's like the brain can't keep doing what it's been doing when the plaques get too much. It tries some other things, it seems to, for some reason it's phosphorylating 205, a different spot. And then the total tau that's released goes up so all tau levels really start increasing close to the time of symptom onset. So we

have a measure called total tab, which just means non phosphorylated tau. And you can measure that, when that's going up. And so these things grow over time, they accumulate over time, until finally, right, when the first symptoms of Alzheimer's disease set in someone, the tau system fails and it collapses and you have aggregated tau. Now you've got aggregated amyloid plaques outside your neurons. And inside your neurons, you have this aggregated tau. And then that plays hell with everything. And then the brain can no longer adapt and compensate.

And other tau forms, one we recently reported on in the scientific literature is called microtubule-binding region of tau 243, I heard somebody say 242, I think they might have meant 243. And this 243 correlates very well with these aggregated tangles inside the neurons, but not with the amyloid plaques. So now we have amyloid markers, and we have tangle markers. So we have plaque markers and tangle markers. And then some of these measures are in between plaques and tangles, they seem to reflect both at different stages. So the good news is, there's now a number of biomarkers in the blood and in cerebral spinal fluid that we can use to track separately and together the plaques and the tangles of Alzheimer's disease. The really important thing about that is, some of our medications like when we remove plaques, they'll definitely remove plaques, but they may not affect tangles as much...or they might.

So now we have a way to track the tangles and the plaques independently. And what we're doing with that is, for example, we have a trial in our DIAN-TU platform for those people, the families with mutations that have very early onsets: thirties, forties, fifties. Those people, some of them are in a trial right now where they're getting a drug to remove the amyloid plaques, and they're also getting a drug to try to stop the tangles. So it's a combination therapy of 2 drugs in the same person at the same time. And we think that's has a chance to be maximally beneficial for people. And we're and we're doing that and other trials under other trials that are getting ready to start for the late onset form of Alzheimer's disease in a similar fashion to use combination drugs. But this is how we use all these biomarkers. So I think as the field progresses and we get more and more of these biomarkers. We're going to be able to really track Alzheimer's in ways that never could before. And if it allows us to do things we couldn't

do before.

NANCY LYNN: It sounds listening to you like it's an incredibly exciting time in Alzheimer's research. But also, it's too much to say the Wild Wild West, but there's still so much to learn. Let's put it that way. So I would just want to say to everybody, if you're confused, you are definitely not alone. And this is also partly why it's so difficult, I think, for people to find a doctor, a general practitioner, who is savvy enough to help them. And I just want to acknowledge, as I have on prior episodes, how difficult that is for people, and that that's part of why we're doing this series so that you have more information over time. It's very complicated. But to be able to push the doctors and I did receive several questions, "How do I convince my doctor to help me get a diagnosis?", "What are the steps I can take?" And I don't know if you feel qualified to answer that, or if there even is an answer, because it is as you said before, it's so individual and depends where you are and what's available to you. But any words of advice there, or is that outside of the lab?

DR. RANDY BATEMAN: Oh, no, I know there is. I mean, you know, there's two ways to do that, I suppose, at least 2 ways to do that. You know, like if I have a patient and they say, well, you know I've asked my doctor to try to diagnose this, but she or he doesn't want to, for whatever reason. The first thing is I always recommend sitting down and clearly talking with your doctor about the reasons you want to know, and about the reasons that they don't want to do a particular test right. So why wouldn't we do this test? What are your concerns? What do you think about this? It's really important, I think, for a patient and a treating physician to really understand each other. And so it may be that a person's doctor isn't comfortable with it because they just don't know enough about it. It may be that they're not equipped to handle the follow on consequences of the test, right. They say, well, I can run the test, but then, what am I going to do? I don't treat Alzheimer's disease, or I don't do this or that. And so it's worth really understanding your doctor and your doctor really understanding you and what it is that you're looking for. And a fair question is, well okay so if you can't or don't do this kind of testing, who does? Where can I go to? Who would I talk to about this? And most doctors should be able to answer that. They should be able to say, well

there's a specialty clinic here, a specialty, doctor there that I can refer you to and give you some advice in that area. If you're not successful in that, and I recognize, by the way, I grew up in a very rural area in mid Missouri on the farm, so I appreciate in rural communities and in other communities, it can be hard to find people with the answers just by talking with people. And so sometimes you have to, you do have to reach out on your own to find those people, and they may not be in your local community. So if you don't get your answer, you know, with your own medical community, your own doctor, then you can go on the Internet. You can ask friends, family, you can contact patient support groups. I mentioned the Alzheimer's Association. There are many ways to find people.

NANCY LYNN: And BrightFocus Foundation, I'll just throw that in.

DR. RANDY BATEMAN: And BrightFocus Foundation, right. So you can ask BrightFocus, and they can tell you where you live and who you can contact and reach out to. There's a lot of opportunities there, because you know, look at it we are diagnosing, but it is new and it hasn't been around very long, and but it's definitely here. It's definitely coming to many other places. So it's a matter of time before most or all doctors will know about this and be able to appropriately refer for it. But I would just say, you know, don't give up. I mean, I think it's important, you know, even putting aside the amyloid removing drugs. It's important in the years that I've been treating people, that people have an accurate diagnosis. And it's always been important. And it's been a bit of a travesty that the medical community writ large, which is more than just the doctors, it's the insurance companies and the government groups and everybody else, have not really prioritize an accurate diagnosis of Alzheimer's disease unless there's something to do about it. And medicine, we diagnose all kinds of diseases, whether there's a specific treatment for it or not. And I've always felt and thought that people who have Alzheimer's disease deserve an accurate diagnosis. And it's not just to settle their minds so they know for sure whether it is or it isn't. It actually helps them and it helps their family manage and cope and move forward with it whether a person has it or not. There's very real benefits, if you think it's Alzheimer's, but it's really not, then you need to find out what else it is because they're

different treatments depending on what it is. But if you don't think it's Alzheimer's, you're not accurately diagnosed, up to half the people aren't even given a diagnosis of Alzheimer's disease, but you really have it, then you're missing out on the ability to understand what's going on. And that, in my experience, causes huge stress and anxiety for the patient and the family members who are just running over their minds: Why is this happening? What's going on? Am I losing my mind? And they don't have an answer. So I'm a big advocate that I think people really need to know what's actually happening. And it's with that knowledge that that people and the medical cares can really take action and help people out.

NANCY LYNN: I'm so glad you brought this up because we did actually receive several questions about you know, what if I got a mistake in diagnosis, or there was a woman on last month who wrote in and spoke with all of us, and said she had been diagnosed with AD, and then she was re-diagnosed with FTD. And I think most people will remember that Robin Williams had been diagnosed with the Parkinsonian type of dementia and upon autopsy his widow Susan discovered he actually had Lewy body dementia. And they were trying to find out, and part of the struggle for them and for everyone is that the symptoms may be different, and the treatments may be different, or the medications needed may be different. And a lot of people really do want to know, and it's so difficult. So I love that you said, keep trying. And I was joking around, but I will say that if you are having trouble getting an accurate diagnosis, getting a diagnosis, getting someone to respond, do call us at BrightFocus because we will, we cannot give medical advice, we're not doctors, but we can try to help you find places that are qualified and could potentially help more. And we do advocate a lot for participation in clinical research, which you know, participating in studies, whether they're for drugs or therefore exercise or sleep, or you know, lifestyle interventions, because getting involved with a research study or a clinical trial are one of the best ways to get the most accurate best care. Especially right now, as the field is just sort of exploding with information and potential treatments which is so exciting. So thanks for bringing that out. Meryl wrote, I'm going to stick to blood for one more question here, "Am I required under law to submit results of a test? Or does it remain confidential?"

DR. RANDY BATEMAN: I'm going to try to answer that in a couple of ways, because I'm not sure what specifically Meryl's referring to in terms of submit test by law. I'm not aware of any law that requires any patient to submit any medical information by law. Well, that's not quite true. So there are things that affect public health maybe an exception to that. But in general no one's required to submit any tests by law, as far as I know, to the government or anyone else. And so but I'm guessing that's not what the question is really about. I think what the question might be about is, if you get a test, let's say you go to a doctor, and you say oh, I want this test to see if my symptoms are due to Alzheimer's disease and you get the test. Is there any way to keep that out of your medical record? I think that's what, cause that's probably, the more common concern is what if I get a test and I find out it's Alzheimer's disease. For some reason I don't want my insurance company, or the rest of the medical system, or someone else to know this. Can I keep it hidden specially? In general the answer is no. If you go in to see a doctor, it's very difficult to get a test through standard doctor prescription, you order the test because it goes into the medical chart. Now, there are very strong laws in the United States that protect the information in your medical chart. So, for example. it's actually against the law for anyone to look at your medical chart who doesn't have a reason to be there, and only for the purposes of what they're looking for. It's called HIPAA, the HIPAA act. And so your doctor can't talk about your test, or the nurse, or anyone else to anybody else, not even your spouse, without your permission. And so the information really is kept quite secure. And the vast majority of information, and Alzheimer's tests are in the same boat, you know are personal and sensitive, and so people are not looking at that. Now, that's the medical system. There are other things, for example, like insurance. So if someone is interested in getting health insurance, there's rules in place that really prevent health insurers from discriminating against people who have pre-existing illnesses. And in general, those work really well, I think. I have yet to hear any of my patients say I was dropped by my insurance company because they found out I had Alzheimer's, or something like that. I've never heard of that. But long term care insurance is different. And so if you don't, if you already have long term care insurance, they can't drop you if something comes up usually. But if you don't have it and you find out you have Alzheimer's, and then you apply for life insurance for long term care insurance,

they actually can discriminate against your pre-existing diagnosis. And that's why they have you fill out those forms and say, are you aware that you have any illnesses? So I would say, I always advise all my patients before any testing, before anything, if you want any kind of insurance, or whatever, get all of it ahead of time. And in general, that you should think everybody should just think about. That's a general advice to the world, you know, whether you're 50 or 60 or 70, think about, you know, will you need, do you want these kinds of things. And if so, it's almost always best to get it before something happens, not after it happens. So those are just some of the considerations that that my patients tend to ask about and so I'm trying to share that. But to answer the question directly. I'm not aware that anybody has to submit anything that anyone else. It's a medical test like any other.

NANCY LYNN: I think you answered the right question. I'm going to move quickly because I can't believe we have nine minutes left. But BrightFocus does research for also macular degeneration and glaucoma and talks a lot about the connection between the eye and the brain. Can you tell us about whether Alzheimer's can be diagnosed through the eye?

DR. RANDY BATEMAN: Not today. People have been working on this for two decades or longer, actually, but even 20 years ago they were using eye scanners to look at the lens, which is just like it sounds, it's a lens that focuses light, right, and so it's where people can get cataracts. And you can have your lens replaced and things like that. And then there's the retina in the back, and that's the part of the eye that actually senses the light and encodes it. So the neurons then from the retina go all the way back into the brain. And so it's actually directly connected to the brain. And so with that connection, you know, everyone's heard the phrase, you know, the eyes are the window to the soul. And so people like to say, well the eyes are actually the window to the brain. And you can look right in the back of the eye, and you can see, it's one of my favorite parts of the neurologic exam is doing the fundoscopic exam, you can just look right into the eye, and you can actually see the retina and the blood vessels and the neurons and everything back there. You can just see it right from the outside. It's really incredible. And so these devices now have gotten very advanced, and they can scan the eye and the retina and the lens and

everything, and come up with all kinds of information. And for 20 years people have been using that try to figure out, can we detect Alzheimer's disease? Can we detect amyloid plaques? Can we detect other processes in the eye? There's been lots of interesting findings, but nothing that has really continuously been shown to work by multiple groups over time. So we don't have anything consistent yet. But it's possible that in the future, you know, it might be possible to just have a machine look in the eye to tell if someone has Alzheimer's or other things and see. But we're not there yet.

NANCY LYNN: That's really cool. And, Michael, I'm going to have you unmuted to ask your question. But I'll also mention, I think the eye exam is fascinating, and there's also all kinds of wearable devices that are being tested. Sensory devices that can detect speech patterns or movement patterns in your body. And there's so much work being done now on these wearable sensors. And question of whether they can, whether in the future we'll be able to detect Alzheimer's disease even from changes in your speech patterns or your movement patterns, the way your muscles move, and I find it very fascinating. But let me let Michael ask a question, although he's disappeared from my screen. Michael, are you on?

MICHAEL: Yes, I am. Thank you so much for this talk and your work doctor. I have to tell you, I never thought we would be where we're at today with the progress that we have made with Alzheimer's. But, as you know, as we've gotten better identifying people with Alzheimer's, we've now also eliminated a lot of people who thought they had Alzheimer's. What is your recommendation for those group of folks who have been tested, let's say in the last 5 years, and they don't have Alzheimer's. What would you recommend for those folks? Would you recommend any continuous testing at this point, or to just wait till the next level of changes that we start to identify other forms of types of dementia?

DR. RANDY BATEMAN: Yeah. My recommendation is, I'm going to give two kinds of recommendations. One is going to be for people who are actually in that situation, right, where...a person's been told they have Alzheimer's, or they have symptoms that are not due to Alzheimer's disease. And the first thing, of course, is to be sure that it's not Alzheimer's

right. So you need to make, we talked about the accuracy of tests, make sure that the test is really highly confident that a person doesn't...if you don't have amyloid plaques, you don't have Alzheimer's disease. That's by definition, okay. So if you have a very highly accurate test, and you can prove that someone doesn't have amyloid plaques, then by definition, that's not Alzheimer's. But that doesn't mean the person doesn't have problems. It doesn't mean that the person doesn't have thinking issues or memory loss or other problems. And so then it becomes even more important, because as I said, with Alzheimer's, there's now a plan of action that's being taken. It's more important to figure out what is it? It's also harder because these latest breakthroughs in Alzheimer's enable us to be more confident on Alzheimer's, but the other kinds of diseases that affect memory and thinking are actually harder to diagnose because we don't have all those tests yet. We don't have a blood test, and we don't have spinal tap tests for many of these or PET scans, right. The PET scans were designed for Alzheimer's disease, so if they show up negative, but they don't say anything else, right. And so what's interesting is that, for example, a couple of scientists, researchers in my group, in my lab actually recently reported a new kind of part of tau that seems to change in a non-Alzheimer's disease dementia called a corticobasal degeneration, or CBD. And what it looks like is that changes in some of these proteins might give us an accurate way to diagnose other neurodegenerative diseases. Other dementias, like CBD. People are working right now on FTD. There's a test out for, we mentioned Robin Williams, there's a test out now that can detect Lewy bodies by alpha synuclein aggregation. And so these tests are coming. And I think in a relatively short amount of time, because this field is just taking off like wildfire, there's going to be a lot of tests that are going to come out that we can use to make accurate diagnoses for people. But there are also common things, right, that aren't the neurodegenerative diseases that can masquerade life in neurodegenerative disease. So, for example, obstructive sleep apnea, if person throughout the night gets low oxygen levels to their brain, it can actually cause thinking and memory problems. Depression, depression itself can cause thinking and memory problems. Thyroid disorders, vitamin deficiencies, infections, toxins, there's all kinds of things they can cause thinking and memory problems. And it's really important at that point to see a specialist, someone who's really experienced in this area, to turn

over every stone to find anything they can for what's causing the problem, because once you find the cause, it's much more straightforward to figure out, can you improve it or treat it? And some of these things you know, we need to treat earlier rather than later. So I would say, don't give up. Reach out to others. Try to see specialists where when needed, and try to get a diagnosis so that you can try to treat any symptoms as best as one can.

NANCY LYNN: That is really fascinating. And quickly, before we go I want to ask our attendees. I was planning to cover, in our next month's episode, things you can do to reduce your risk because we've had a lot of questions about that. But I'm going to give you guys a chance to vote in the chat box. Since we're talking about all these different kinds of dementia, which is really quite fascinating, and ways to detect these different kinds, whether you would rather next month to hear about ways you can reduce your risk or what are the different types of dementias. And we will get to both, but if anyone has a really strong preference for which we do first please type it in the chat box. And Dr. Bateman, I'm going to make you promise in front of all of these people that you will come back and speak with us again, after you've done your 1,300 page grant submission, which he is working on today. And so I want to thank you for taking time out of your day as you're working on a 1,300 page grant submission to do this for us, for BrightFocus, for our donors and supporters. And if you guys can...so thank you real from deeply from the heart, if you can bring up the slides. If your question wasn't answered, we're going to send you these resources and other additional resources about the diagnostics field. There's a wonderful article, several good articles on all of the new technologies coming out to diagnose dementia. And so we're going to send resources to everyone. And this whole program will be available on recording in about a week or two, once Alexa has time to edit everything together.

If your question wasn't answered, please feel free to email us at reply@brightfocus.org and if you can go to the next one. We also offer free publications about Alzheimer's disease, and if you are interested in receiving those, again for free, there's a number to call. We'll be sending this to you an email as well or you can email info@BrightFocus.org. The link below that, the www.nia.nih.gov/health/how-alzheimers-disease-

diagnosed is an article that covers a lot of what's happening in the world today, or yesterday maybe, seeing how fast things are moving in the field of Alzheimer's diagnosis, and we're going to link to that on our website, BrightFocus.org/Alzheimers.

This is our fifth episode, we're going to keep doing these monthly and as promised in, I think, the second episode, we are going to start to do another series called "Zoom in on Research" where we can actually review different trials that are available, and how you participate in a trial, what types of research you can participate in and really walk through those things. But if you want to see a prior episode, for example, we did do one episode on FTD, you can go to brightfocus.org/ZoomIn. And all the episodes are also available in their entirety on YouTube. I think that's it. If you can go to the next slide. Our next episode will be on October 19th. And I wish everyone a great month in between then. And again, if you have a burning question, please do feel free to call us or email us. We'll be happy to try to address it as best we can. Once again, thanks Dr. Bateman, and I hope everybody has a great week and a great month. Take care.

DR. RANDY BATEMAN: You're welcome. Thank you all. Bye.

Useful Resources

BrightFocus Foundation: (800) 437-2423 or visit us at BrightFocus.org. Available resources include—

- How is Alzheimer's Diagnosed?
- How Biomarkers Help Diagnose Dementia