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

The Role of Genetics in Early Diagnosis and Treatment of Dementia
Thursday, June 20, 2024 | 1 p.m. EDT
Transcript of Zoom with Stephen Salloway, MD, MS
Professor, Alpert Medical School of Brown University and Associate Director of the Brown Center for Alzheimer's Research

NANCY LYNN: Welcome. Welcome to Zoom In on Dementia and Alzheimer's. I'm Nancy Lynn with BrightFocus Foundation. BrightFocus Foundation funds research globally for Alzheimer's disease, macular degeneration, and glaucoma. And we have invested over $300 million supporting scientific research worldwide. So I'm delighted to bring you this program today with Dr. Salloway. Just want to let everybody know that this program is supported by very generous educational funding from Alzheon, Biogen, Lilly, and Genentech. So welcome. It's a great topic today and an amazing and wonderful guest. For questions that came in that are not on this topic of genetics and early diagnosis, just want to refer you to the online library of episodes that we've done so far where a lot of other types of questions are answered. But since people are being diagnosed every day, they never get old. So if you want to look at something like the new drug Leqembi or how Alzheimer's disease is diagnosed, these are free and they're online at brightfocus.org/ZoomIn and on YouTube.

So terrific, I'm going to jump right in because we have a lot to cover.

And I'm going to introduce Dr. Stephen Salloway. Dr. Salloway is an internationally recognized leader in clinical trials for the prevention and treatment of Alzheimer's disease. He received his MD from Stanford Medical School and completed residencies in neurology and psychiatry at Yale University, in other words, he was slumming it. He is founding director of the Memory and Aging Program at Butler Hospital, Associate Director of the Brown Center for Alzheimer's Disease Research, and Professor of Neurology and Psychiatry at the Department of Psychiatry and Human Behavior, Warren Alpert Medical School of Brown University. So welcome, Dr. Salloway. It's a pleasure to have you.

DR. STEPHEN SALLOWAY: Thank you, Nancy, for inviting me.

NANCY LYNN: So I'm going to jump right in and say, it's well established, we know that genetics are involved with getting Alzheimer's disease and other dementias, though, we know genetics are not the only factor that affect your risk. But can you just start us off with a broad overview of what we know generally about genetics and Alzheimer's disease?

DR. STEPHEN SALLOWAY: Well, maybe I could start with even a higher level overview about Alzheimer's disease and how we're at a transformational moment and, really, in the diagnosis and treatment of Alzheimer's, entering a new molecular era. And genetics have played a big role in that. And so it might be good for the audience to have an appreciation of how things have evolved in a very quick overview.

So Dr. Alzheimer was a psychiatrist and neuropathologist in Germany at the turn of the last century. And he was a very inquisitive person. He was interested in memory trouble and schizophrenia and alcoholism and what the mechanisms were, and very much based on the phenomena that he observed in patients and then studying them, studying their brains whenever he could. He had a really advanced neuropathology laboratory at the time, which is not typical of psychiatrists today. They usually don't have a dual training in neuropathology. And he encountered a woman who was 51 years old in early 1900s. And she developed severe memory loss and terrible change in behavior and died about four years later. And he studied her brain using the techniques that he had available. And he reported her case, an initial case in 1907, as a case of-- it wasn't called

Alzheimer's at the time, but it became known about 10 years later as Alzheimer's disease-- but a case of dementia, which was due to plaques, which were known, and tangles, another protein which had not been previously identified. And that combination of plaques and tangles, those clumps of proteins have remained the hallmarks of Alzheimer's disease since 1907. Now, when he gave that case presentation, he was shouted down. The audience said, that can't be. You don't know what you're talking about. And that's what often happens when you make a discovery. It upsets the status quo, and people push back against it. But it's obviously held up over time. And it turns out that that first patient had a genetic form of Alzheimer's disease. So he didn't know it at the time. We didn't know that there were highly genetic forms, mutations that cause Alzheimer's. But it turns out she has what's called a presenilin-2-- she had what's called a-- they studied her brain years later when we had the laboratory test. She had a presenilin-2 mutation that caused that early onset of Alzheimer's in her case.

Now, Dr. Alzheimer reported very few cases because people didn't live very long. The average life expectancy at that time was 50 years. And so it was thought that Alzheimer's, this form of dementia, was rare. But now that we're living longer, it's really aging is the biggest risk factor for Alzheimer's. But genetics is a very important contributor. So when we first began to take this more seriously in studying Alzheimer's disease in the 1980s, a clinical criteria were developed that were all based on just the symptoms of Alzheimer's. There were no biomarkers. There was no MRI. There was no PET scans, none of these sophisticated tests that we have now.

NANCY LYNN: Sorry, Dr. Salloway, what's a biomarker?

DR. STEPHEN SALLOWAY: A biomarker is a test like an MRI scan or a blood test or a PET scan where you identify, hopefully, as precisely as you can, the specific pathology that-- or at least confirm that that pathology is present in that patient to make sure-- that's what we do in cancer now. We anchor the diagnosis in the molecular form of that cancer and then target that with treatment.

NANCY LYNN: So you're seeing the protein.

DR. STEPHEN SALLOWAY: Being able to see the protein and the specific type of protein or the specific genetic form, whatever it is. So early on, though, a diagnosis of Alzheimer's was clinical based on symptoms. So someone had to have dementia to be diagnosed with Alzheimer's. And then, if they died and you looked at their brain, it was confirmed on an autopsy. I tell you, the next big step, that next big advance was genetic where we identified there are three different mutations that can cause early onset Alzheimer's, like Alzheimer's first patient. She would have fit into that category. And that allowed us-- it's only 1% of patients with Alzheimer's have a mutation causing their disease. But scientifically, that is so valuable because you can now take that mutation and produce animals that have Alzheimer changes and then test drugs to see if you can reverse or protect that animal from developing the neurodegeneration, the loss of nerve cells that goes on with Alzheimer's.

So genetics played a huge role that started in the 1980s and included Down syndrome because it turns out that one of those mutations is in chromosome 21 for the amyloid precursor protein-- that codes for the amyloid precursor protein. And patients with Down syndrome, or people with Down syndrome, have three copies, have an extra copy of that chromosome, and most of them go on to develop Alzheimer's disease. So that was really-- having those mutations really been helpful scientifically. And now we've been studying-- you heard from Dr. Bateman in this series, Randy Bateman, who's head of the DIAN Program. We actually study patients here, around the world, and also a special population in Colombia that have these mutations. And we can detect the earliest changes in the brain with Alzheimer's because we know, if someone carries a mutation, 100% chance they're going to get Alzheimer's. And we know approximately it's about the same age as their parent who had the disease. And so we can then study, starting at age 18, what are the changes that occur in Alzheimer's disease that we can detect and then keep improving our detection of those. So genetics have played a huge role. And as a result, we now know that the plaques of Alzheimer's, which are made up of amyloid protein, begin to accumulate 20 years before the memory loss. So the clinical decline is really a late stage of Alzheimer's. All these changes that are going on in the brain, starting with amyloid plaques. And then tau tangles, tangles made up of tau protein occur closer to the

time of memory loss. And then you get changes on MRI and other tests and clinical changes. So that was, genetics played a big role. Another big genetic-- and I'm sure people are going to ask about this.

Another big advance in the early 1990s was the identification of a risk gene called the APOE4 gene. That doesn't mean you're going to get Alzheimer's. But it means that you have one or two copies of that gene, you have a higher chance of developing Alzheimer's. And we can now test for that with a blood test or a cheek swab. And it turns out it makes a difference about the age of onset of Alzheimer's if you carry one or two copies, how you might respond and your safety risk with the new drugs that lower amyloid protein. So that was a big advance. And people need to decide. And I'm sure people will ask about this on today's session, should they be tested for that? Because that's a test that you can do on your own through 23andMe. I don't recommend it, because you don't have the counseling that would be helpful to go along with it to help you interpret it. But it is available either direct to consumer, or you could come to our program or many other memory programs and have that test done, if that's right for you and we all have to decide that if it makes sense for us. So then, the next step forward was biomarkers. So Nancy asked me, what is a biomarker? How can we document these changes? I said there's changes in amyloid. There's changes in tau. Can we measure that? Can we determine for sure that that's going on and what stage the disease is at? And it started in the 1990s with spinal fluid, looking in spinal fluid. There were tiny changes in amyloid protein and tau protein. As the amyloid builds up in plaques, there's less of it in spinal fluid. As tau protein leaks out of nerve cells, as they start to decline, it goes up in spinal fluid. And we start to be able to measure that. And now this is actually a clinically available test to see if someone has the changes of Alzheimer's disease. That was a big step forward.

In early 2000s, a major step forward was being able to see the plaques, the amyloid plaques with a PET scan. And that was the first time we were able to safely see those. And now those there are three tracers approved by the FDA for that. 10 years later, we can now measure tau protein with a PET scan. There's one tracer approved by the FDA for that, does a very good job of that. And the most exciting thing is now we have blood tests

to do all of these things. We can see the changes in amyloid and tau many years before the memory loss with a blood test. And they're looking really good. This was elusive for years. We went to meetings every-- oh, we've got a new blood test. And then it would fail. It didn't hold up. But now there are a number of assays. There are a number of different tests that, they're just as good as a PET scan. They don't tell you where the amyloid is in the brain or where the tau is. The PET scan has that extra value. And you can't measure exactly how much there is in the brain, which you can with a PET scan. But it can tell you if the PET scan is going to be abnormal. And so it's a good way to confirm-- a simple way, really to confirm that there's Alzheimer changes that person's experiencing.

NANCY LYNN: So I'm going to want to back up a little bit. So all these different diagnostic tests-- a PET scan, pulling spinal fluid, the blood tests for amyloid and tau, they are detecting amyloid protein or tau protein, which is a biomarker or a sign for Alzheimer's. Are these different than, say, specifically genetic tests?

DR. STEPHEN SALLOWAY: Yes. Those are not genetic tests. Those are tests for specific proteins that build up in Alzheimer's. And they don't test a gene. Specific genetic tests would be, if you came from a family with onset of Alzheimer's at age 50 in multiple family members, we'd be concerned that you have one of these mutations like Alzheimer's first patient. And there's a genetic test for each of those mutations. Typically, it's a blood test. And we can tell, do you have one of those mutations or not? That's a specific genetic test, but we only test-- now, I want to be clear about this. We only test people who have a certain family history of early onset Alzheimer's and multiple family members. And that early onset means around age 50 or even earlier. So it's not very common. We don't do that test very often. And often, even if a person has that history, their insurance won't cover it. It's crazy. So that's a problem. So the whole insurance issue is a major issue, which we have to keep moving forward. And think this audience can do a lot. We all need to be advocates. This is one of our most serious public health problems. And we all need to work together to move it forward. So that's a specific test. Another genetic test, another specific genetic test would be for APOE4 genotype. And that doesn't tell you about amyloid or tau. It tells you if you carry zero, one, or two copies of that risk gene and whether or not you're at higher or lower risk. But it doesn't measure the proteins of amyloid or tau or any other

abnormal protein.

NANCY LYNN: I'm going to ask you to talk a little bit about APOE4 and presenilin-1 and 2, so that we understand what the different things that people are going to be looking for. But I'm very interested to make clear-- and I've been doing this for 15 years, and I'm not clear. If somebody wants to get genetic testing for Alzheimer's, what can they do? What can't they do, at what ages? Someone even asked, when should we have our children get tested? And to your point that these proteins are building in the brain up to 20 years before any memory symptoms even become apparent, which is good news in the sense that you can potentially treat this disease way before you have Alzheimer's or visible Alzheimer's symptoms-- so going back-- because I was doing my little research, and it said, a few years ago, we knew of maybe 10 genetic variations. Now we know of 80 that are associated with Alzheimer's. So what tests Can people try to get to understand any of these genetic variants if they have them?

DR. STEPHEN SALLOWAY: OK, Nancy, there's not a simple answer to that. I'll try to break it down as best I can. The field is changing. We're in a period of transition. So I'll give you some clear examples of when someone may need to or want to be tested. So we now, as you know, have a new medication called lecanemab that's approved for the treatment of early Alzheimer's. It's for people who are building up amyloid plaques and already have some cognitive difficulty but are still functioning well. One of the side effects of that medicine can be fluid shifts or brain swelling or small amount of bleeding in the brain. And we need to test for APOE for everybody before they go on that treatment. That way they can weigh the risks and the benefits because the rate changes if you carry two copies of APOE4, and the rate of a more serious reaction goes up. So people need to know what the risks are. And then the doctor needs to know how to monitor it. So having that information about APOE helps. So everybody who's considering treatment with lecanemab-- and we hope soon there'll be another medicine called donanemab that will become available, had a positive review last week from the FDA advisory committee. Those patients will need to be tested for APOE also. So that's a really clear case where everyone should, who's considering that seriously, should be tested for APOE. If you go into a clinical trial, there may be a

trial that's specific for people who carry APOE4 or two copies of APOE4. We've done trials like that. There are trials ongoing like that, and so that's another reason. And increasingly, we're sharing that research information. Previously, it was considered a research test. But since these things are now clinically meaningful and we understand them better, we're disclosing them more often. So someone who's considering a prevention trial, who might be at higher risk, will probably have their APOE genotype tested. So that's another good reason that people may want to find out, and it may qualify them or not for a trial, depending on the criteria. For people who want to-- are concerned. So those are the most clear cut for APOE. And the same-- it's another easy one. Well, not easy, because of insurance, but generally it's easy, if someone comes from a family with multiple members with early onset Alzheimer's where there could be a mutation, then that person may want to be tested. That's be a good reason to be tested.

NANCY LYNN: And early onset-- so early onset is usually 40s, 50s, 60s, whereas—

DR. STEPHEN SALLOWAY: In this case, it's going to be 40s and 50s. We also call early onset without a mutation less than 65. So there's 5% of the population with Alzheimer's are 65 or younger. 95% are 65 and older. So age is the biggest risk factor. But 5% of people, and only a small percentage of those will have a mutation. So they have another form of early onset without a mutation. What I'm talking about now is even earlier, so 50s and 40s, that multiple family members where it's inherited. And if there is a mutation in the family, it's a 50/50 chance that a child of that parent will develop Alzheimer's. If they have the mutation, they will develop it. If they don't have it, they won't develop it.

NANCY LYNN: Right.

DR. STEPHEN SALLOWAY: So that's another specific test and a clear indication that people may want to pursue. But barring all those, now we get into more of the gray area and also the access issue. Anybody can do 23andMe and obtain-- if they-- I think you might have to check a box to get APOE. But you're unsupervised. You're on your own with that. And as I said before, I don't recommend that, but that is available to people. That's direct to consumer. It's just a problem you don't have assistance in

interpreting, what does that mean for me? And what treatment options are now available to me and whatever? What should I be doing now that I know that, especially if you're at higher risk? In our program-- and we'll hopefully we'll get to the address, we have a prevention registry. It's called the Butler Hospital Alzheimer's Prevention Registry. And people can sign up. I think we start at age 50. And they have an opportunity to learn about their-- they may have the opportunity to learn about their APOE status and get counseling for that through a research program, and there may be others around the country as well. A person could talk to their family doctor who probably won't be familiar with this yet or a neurology specialist, who will increasingly become familiar with this. And there they may have access. And certainly, there may be other memory centers where they could find out. The other thing people want to do is come to a prevention registry like ours. And there are a number of them-- you don't have to just restrict yourselves to ours-- and find out what research is going on, what options are available to them. You're not obligated to do anything if you sign up. So it'd be good to learn more. And there are a number of them around the US, different prevention registries or Alzheimer's registry.

NANCY LYNN: And I think-- and we'll send everybody who registered for this program an email in about a week from now with the recording of this. And we can put in links. I'm looking at my trusty Amanda. We'll put in links to some of the bigger registries.

DR. STEPHEN SALLOWAY: That'd be good.

NANCY LYNN: Certainly, to Dr. Salloway's registry because this is a great way to also get current information on a regular basis. When you're in a registry, you tend to get more informed, at least, that's been my experience.

DR. STEPHEN SALLOWAY: Totally, totally. That would be good to give people a number of registries.

NANCY LYNN: A couple of questions that are coming into the chat, in no particular order-- so you always hear a concern, well, if I get testing to see if I have two copies of the APOE4 allele or any other genetic variant, is this

going to affect my insurance? Is it going to be a preexisting condition? Can you address that?

DR. STEPHEN SALLOWAY: Well, that is a concern. And right now preexisting conditions are covered. So it should not affect your health care insurance. But that protection does not apply to long-term care or life insurance. So if you don't have those, and you go to-- I don't think, right now, to my knowledge, insurance companies have not been focusing on this. But things could change, and they could ask that information. Have you been tested for APOE4? What is your genotype? They could factor that into their decision about coverage. So it could potentially affect your insurance, those insurance, those types of plans. One thing we try to do, as best we can through research study, is keep that information confidential. That's a research done through research. It's not part of your clinical record unless you choose to inform your family doctor or whatever. And so we try to shield people from that risk, but that is a potential risk people should factor in. So if they're really concerned and they really want to get that type of coverage, get it before being tested or before putting anything in their medical record to be on the safer side, if they can.

NANCY LYNN: We're getting a lot of questions in the chat about the blood tests, about C2N's Precivity tests, and blood testing versus other more invasive types of testing like the spinal fluid. So question one is, are blood tests readily available? Can people get the blood test now? And again, the blood test is not necessarily showing your genetic risk. It's showing your proteins, your amyloid proteins in your tau proteins?

DR. STEPHEN SALLOWAY: It says, do you have what those tests do, generally, do you have evidence of Alzheimer's pathological change? Do you have build-up of amyloid in the brain? And they're pretty good at predicting that with a high degree of accuracy, either yes or no, not 100%.

NANCY LYNN: And can anybody get that at this point?

DR. STEPHEN SALLOWAY: But now we're in this period-- again, I'm going to sound like a broken record here with this period of transition thing. But the tests are now becoming available. I think any clinician can

order the C2N Precivity2 test, which is a really good test. It's not currently covered by most insurances, so the person will have to pay out of pocket. It's not as much as a PET scan, but it's not cheap. So there is a financial consideration there. It's not FDA-- they increasingly are laboratory-certified tests, so they've gone through a validation study. But none of them are yet approved by the FDA, which would be good. It'd be good to have both those things, FDA approved and coverage by Medicare and Blue Cross and other insurance providers.

NANCY LYNN: Yeah, they're still just moving toward that, right?

DR. STEPHEN SALLOWAY: We haven't achieved that yet. We need more advocacy for that. We need to push these companies to do the legwork. It's a pain in the butt to get all that stuff done, that regulatory hurdle to get that approval. The tests are good enough to be approved, in my opinion. But they've got to do the legwork to get the approval, and we all have to push. I don't know why we have to push because, if I were Medicare, I'd say gee, I could do a blood test for $500 to $1200, or I could do a PET scan for $5,000 to $8,000. Wouldn't it make a lot more sense to do-- if the blood test is pretty close to as good, let's do the blood test, especially at least to screen, see who needs a PET scan? But for some reason, we get our heads backwards. I think the insurance companies should be taking the lead. They should say, boy, it's going to be way more cost effective and way more available. Let's get the blood test into the clinic. But we haven't quite gotten that urgency, that accelerometer yet, even though the tests looked good. But doctors can order them.

NANCY LYNN: Right.

DR. STEPHEN SALLOWAY: Now, question is, who should get it? And who's going to interpret it? And what does it mean? So I wish I could give you easier answers, but I want to be very frank with the audience about where we're at. The ultimate goal is to-- primary care is very good at screening for a variety of major diseases. That's what they do. And we have to get them educated and engaged in this whole process so that they can-- because that's where patients are. They're with their family doctor. And that's where this screening should begin, ultimately. We

haven't quite gotten there yet, but that would be really terrific. If we want to confirm-- what I'm so excited about is that we now have the ability-- when a doctor makes a diagnosis of Alzheimer's disease in primary care, they're right about 58% of the time. When a specialist makes a diagnosis, they're right about 72% of the time. But you can get a blood test, and you're going to be right about 94% to 95% of the time. So this is a big step forward where we have-- you take the history, you determine is there cognitive impairment? Could it be due to Alzheimer's? And then, if you do think that's the case, then you confirm it, yes or no with a blood test like we're talking about. But first, you have to do the assessment first. Is there a cognitive difficulty? Is it likely to be Alzheimer's? And then you do the test. You don't just order the tests on lots of people. Right now, we haven't really gotten into any standard of care yet of how to use this test. So that's going to take-- there's going to be a really good paper coming out. I'm writing an editorial about it right now in JAMA about this, about using blood tests in the clinic. And there are increasingly numbers of papers coming out. So it's going to be covered in the news continuously. This is a transformative moment for society to have Alzheimer's be a treatable condition and diagnosed early, that's a major league change.

NANCY LYNN: It's amazing.

DR. STEPHEN SALLOWAY: It's a revolution, really. But we still have a lot of work to do to get our new tests and our new treatments into clinical practice. So it's not easy for someone. Anyone on this call could go talk to their doctor about it or talk to a specialist about it. And they may or may not be appropriate, and they may or may not be able to get the test. But then the doctor has to know how to interpret it, and something new.

NANCY LYNN: Yeah. I want to thank you for being so frank and to say to the audience that, if you are frustrated in trying to understand all of the nuances and how to get a test, how to participate in a clinical trial, will something be reimbursed, you are not alone. It is not you. The system has just not caught up, honestly, yet with the progress that's being made. And all of us in the field and all of the scientists in the field share the frustration that you feel as patients and families because we are also patients and families. So I'm just going to thank Dr. Salloway for telling it like it is. Because a lot of people feel so helpless and frustrated because they can't navigate how to get help, how to get information. And that's part of the

reason for us doing this program is to say, can we just ask the expert the question? I want to—

DR. STEPHEN SALLOWAY: Can I say one more thing about that? Because I know this is a focus on genetics, but everything is all connected, all the parts of Alzheimer care. And we're at this transition point. You mentioned a key word is navigation. We need to do way better. Our program has not focused on that because we've been focusing more on the biology and the biomarkers and the treatments. But the care aspect is so compelling and so urgent, the need is so urgent. When someone gets a diagnosis, they really need to have a care navigator starting from the time of diagnosis, hopefully until the time they die and the family gets the support they need so they know how to manage this. And that's the only way—

NANCY LYNN: It can be 10 to 15 years.

DR. STEPHEN SALLOWAY: It's going to be a number of years at a minimum, and it could be many years, and especially if it's diagnosed early. And the only way we're going to get primary care into this game in a major way is providing them the-- they don't have the time to provide the navigation. It wouldn't even make sense in terms of their time. But they need-- the patients and the families need the navigation, like you're saying to understand this. And how do I navigate? How do I get the support I need? How do I get the tests I need? How do I get in the research I need, et cetera? We're doing this increasingly with other chronic diseases. With cancer, often, in a cancer research program, they get a navigator. Someone is diagnosed with cancer. They're on a treatment regimen. And they get a care navigator, a nurse or someone else who is really familiar with them and is really accompanying the patient and the family, joining with them. We need that. That's the only way we're going to actually bring all of this, all the good, all these wonderful advances and make them available.

NANCY LYNN: I think the care navigators is a new category that-- for Alzheimer's is new-- that really has to grow in the future because this is such a long and complex disease, and we're still learning things.

DR. STEPHEN SALLOWAY: Totally.

NANCY LYNN: And we'll be learning things for the next number of decades that will constantly change. And I want to just address Lynn's comment in the chat where she says, sadly, many of us do not have family, no navigator, and that denies access to many clinical trials. And I think that is one of the gaps that philanthropic organizations like ours tries to fill. You can write to us. And we can't give medical advice, but we can try to say, OK, we'll help you find a clinical trial near you so that you can go and get connected to better information because there isn't a navigator near you. But there are a lot of resources. So if you are in a situation, like Lynn, like you're saying, you can always write to us. You can write to reply-- or we'll have this at the end of the program, reply@brightfocus.org. And we will try to steer you to a local resource. And that's what, ultimately, navigators will help do is get you to a reliable resource locally. Dr. Salloway, I want to move a little bit and go back to your talking about-- we were talking about testing and getting tested for these things. And I want to talk more about that and more about clinical trials and how people can participate in clinical trials if they are APOE4-positive or have another variant. But as we learn more and more about the genetics, how is this, do you think, going to affect both treatments, that there'll be treatments that are specifically targeted to these different variants? And also, potentially, will there be prevention strategies that are tailored to different variants or just helpful for everyone?

DR. STEPHEN SALLOWAY: Yeah so the answer is yes and yes. We're going to have yes to all those things. Well, increasingly, we're going to hopefully have precision-medicine approaches where-- one thing I'm so excited about that we're now able to start to do molecular staging of Alzheimer's disease like we do with cancer. So when someone comes in, either with a memory complaint or not, and they want to find out more about their risk and they may be a candidate for a trial or a treatment, an approved treatment, we can use PET scans, like I mentioned, spinal fluid or a blood test and say, gee, are you building up amyloid plaques, and to what degree? It's not either/or. It's on a continuum. Are you building up tangles, yes or no, and to what degree? And so our new diagnosis, our new diagnostic approach to Alzheimer's is biological. So I told you the first diagnostic criteria were all clinical. You had to have dementia, and there really wasn't a biomarker component. We didn't have the tests available.

And now it's the opposite. We do a biological diagnosis. We try to determine the amyloid status of the patient, the tau status of the patient. There are other proteins that contribute to Alzheimer's disease. There are vascular changes, inflammation. We want to enrich our diagnostic framework with all of these components of the cognitive syndrome that contribute to cognitive change with aging and be specific and then target them. That's where it gets to the essence of your question. You do the molecular profiling of the individual. And you say, oh, you have this form or this risk. And the key component is amyloid or tau or whatever it is. And we're going to target that and with increasingly specific treatments, hopefully, that are effective for that and combine them with other components or other ways to add to the initial effect of that, the first treatment. And that's going to be exciting. That's why I've always wanted to do is bring Alzheimer's disease into the modern field of medicine where we treat it like other major diseases with an early and accurate diagnosis with molecular conformation. We introduce treatments to either slow it down or prevent it and start it as early as we can. Because the earlier we treat a problem like this, the more effective we're going to be. And then, for people who do get affected, who get impaired, we have a whole coordinated system of care. So they're not on their own. They don't have to just figure this out. We can actually provide the support and the care they need. And we reduce the risk. There may be some lifestyle changes that can be very important, healthy-- to promote brain health that we can combine with all these other more biologically focused treatments. So that's where we're at. We're at the beginning stages of that. It's exciting. But we still have way more to do to bring that about.

NANCY LYNN: There are companies and like the one that's sponsoring this program, Alzheon, that are developing or trying to develop treatments that will be that are targeting something different than what Leqembi and donanemab, the ones that will like are approved or and will likely be approved. And so you're saying that those together will be sort of a cocktail where you can try-- or potentially be a cocktail where you're trying something earlier downstream. You're also doing lifestyle interventions-- getting enough sleep, eating a healthy Mediterranean diet, getting extra certain types of exercise, not being socially isolated, getting your hearing checked, all of those things that can help, even if you have a

genetic variant, can help, not necessarily prevent, but postpone-- prevent and postpone? Tell me what I'm saying.

DR. STEPHEN SALLOWAY: No, you're saying-- that's right. I think all of us should be-- listen, let's cut to the chase. If we keep our hearts healthy, we're going to decrease the level, certainly, of heart disease and stroke, and we lower the rate of dementia. So all the risk factors for heart disease-- high cholesterol, hypertension, diabetes, smoking, inactive lifestyle, et cetera-- if we can keep our heart healthy, we're going to keep our brain healthy. So we all need to do that. And we need to start early in life and keep doing it and keep going to keep-- because we want to live a full life and a healthy life so we can enjoy the later years of our life and not be bogged down by diseases like Alzheimer's. So we all need to do that. And some people are at higher risk for Alzheimer's changes, biological changes, and they're going to need more. They should do that, too, but they're going to need more and start it as early as we possibly can. And we have some initial treatments. They have a proven clinical benefit. It's mild. We need to do better. We're going to need-- ultimately, we're going to need combination treatments and hopefully tied to the person's particular molecular type of Alzheimer's. So we treat their disease as effectively as we do with cancer. And increasingly, we treat certain types of cancers with specific targeted treatments. And we're going to do the same thing for Alzheimer's.

So you mentioned there are companies developing-- the sponsor of this program has an oral drug that decreases a smaller form of amyloid before it forms into the plaque. It's targeted for people who carry initially two copies of the APOE4 gene. And they've recruited a cohort of people that have two copies of E4. And then we'll read out, I think, next year. And we'll see if that's effective or not for that population. We did a study called the Generation Trial for people who are E4-- who carry two copies of E4, started with that, and then one copy of E4 and one non-copy of E4. And we recruited a large-- we tested a large number of people for APOE. And these, for people who are cognitively unimpaired. So it was really a prevention trial. And we tested two different drugs for that. So it is possible to target a specific population.

There's another really exciting study. It's teensy tiny, but it's a genetic-based treatment where people who carry two copies of E4 are actually-- they use a viral vector. They use an agent to get a copy of E2 that lowers APOE2, that lowers the risk of Alzheimer's. They inject it into the cisterna magna in the neck to try to offset the two copies of the E4 with a genetic replacement. Again, very small numbers of people, but it's exciting that we're even attempting it. Another treatment I'm really excited about that has helped other neurologic conditions is a gene, a type of gene modification, where we take patients with early Alzheimer's, and we give them-- it's almost like the COVID vaccine. We give them an anti-- it's a funny name, an antisense oligonucleotide. We inject the medicine. Right now, we have to do it into the spinal canal to get enough medicine into the brain. And it decreases the buildup of tau protein. And early days. We're only in a Phase II trial, but it looks like it lowers the buildup of tau protein on a PET scan. That's the first drug we've had that shows that. So it's at least encouraging. And a question, maybe a hint of a clinical benefit early on. But exciting times where we actually get right to the disease process itself and not treat a peripheral manifestation of it and try to shut it down. And ultimately, where I see us going in the next 5 to 10 years-- it's moving quickly, much more quickly than I thought. And thank you for all your support from BrightFocus and other philanthropic organizations and foundations and the NIH and so many groups. We're already doing this with families who have a mutation. So a new study, a new primary prevention trial is underway in families where we know they're going to get it. They have a mutation. We take them from between 10 to 25 years before the symptoms, before there's much amyloid buildup. And we give them the medicine like the one that is about to get approved to block the buildup of plaques or remove the plaques and try to shut it down, either prevent it or substantially delay the whole process. Don't get the tau protein stimulated into clumps. Keep the brain healthy. So we're treating them way upstream before there's any symptoms, 10 to 25 years before symptoms. We're going to do the same thing with people at risk who don't have a mutation. We need the markers. We need the amyloid test or protein marker to say this person right now doesn't have amyloid buildup, but they're at high risk over the next few years of starting to show that buildup. And see if we could give-- I'm just throwing this out here-- a mechanism, a vaccine. Why don't we give them a vaccine against

amyloid or tau? Shut it down. Don't let that build up even start. And see if we can prevent Alzheimer's. So it's coming. And genetics definitely play an important role in this story.

NANCY LYNN: Two things that struck me as you were speaking is, when you talked about the viral vector potential treatment, that there is a genetic variant there or that is actually protective. So not everything we learn about genetics means that this is going to be bad for a person. It could mean something more protective. And I also want to point out-- and someone asked a question about this in the chat. If you do a test and find that you have amyloid, and if you do a test and find out have APOE4, two copies of-- this is not a definite-- this does not definitely mean you are going to develop Alzheimer's or any other dementia. It may mean you're at higher risk. But it is not a certainty. Do you want to comment on that, Dr. Salloway? Because I think that's—

DR. STEPHEN SALLOWAY: No, that's right. And well, specifically with APOE, I mean, it's a risk gene. It's unlike the one I told you with the mutation. If you have a mutation, you will get it. So that's called a—

NANCY LYNN: A specific mutation, yeah.

DR. STEPHEN SALLOWAY: Yeah, the ones I've been talking about for Alzheimer's. And every disease has some form of this in a small percentage, usually. But we call those-- those are deterministic mutations. That means, if you have it, you're going to get it, and it's a predictable age of onset in your family. If you don't have it, you're not going to get it. If you carry one copy of E4, you're at higher risk, about two to three times higher risk of developing Alzheimer's than if you don't have an E4. But you can live out your whole life and never get Alzheimer's. If you carry two copies of E4, you're a substantially higher risk. It doesn't mean you're definitely going to get it, but your chance now goes up higher. So it's more concerning about developing Alzheimer's. And the age of onset of the symptoms, the memory loss is earlier. So if you have-- people should know, if you're going to consider being tested, you should know what you're being tested for. So if you carry two copies of E4, the average age of onset of-- doesn't mean you're going to get it. But if you do start having symptoms, the average age of onset is around age 65. If

you have one copy of E4, you're less chance of getting it, but higher than no copies. The average age of onset is about 75. So actually, I think it's 68 for two copies and 75 for one copy. And then, if you have no copies, you can still get Alzheimer's. But the average age of onset is 85. So it's a whole different situation in terms of your lifespan and your freedom from Alzheimer's disease based on this. But so it doesn't mean you're definitely going to get it, but it tells you more about your chance of developing it and when the symptoms might begin if they do.

NANCY LYNN: Question from a YouTube viewer, Kara, and she says, is there any genetic testing for families with dementia where they have a clear family connection, onset typically in the 70s-- aunt, mother, grandmother-- so a lot of people in your family, but they don't have disease biomarkers. Are there tests or trials for people who just have a lot in their family?

DR. STEPHEN SALLOWAY: And in that question, have they been tested for any of the amyloid, tau, APOE? Well, I can say, that family, it would be very unusual for them to have a mutation. It's never zero in medicine. Everything happens in the world. But it would be unlikely, even with multiple family members in their 70s, it would be unlikely due to a mutation that causes early onset. So they don't-- unlikely to have that. They could be carriers of APOE4. I don't know if that family has been tested for that.

NANCY LYNN: No, I don't know. And she did say onset typically in the 70s.

DR. STEPHEN SALLOWAY: So that could be related to APOE4 but may or may not. And there are other genes too we haven't discovered yet. But in some families we don't really nail down exactly what it is. But there are multiple families have members affected. For that situation, hopefully there is a trial that, either for people who are cognitively unimpaired but concerned or are starting to have cognitive symptoms. Hopefully there are. Well, they may be eligible for some of the new treatments that remove the plaques. If it's early Alzheimer's, then they may be eligible for that. Or they may be eligible for a clinical trial. Or now we're actually going to be starting to do trials with testing medicine and also using the currently available new antibodies that lower the plaques, so combination

therapy. We're already doing one of those. And actually, there are a number of them I've started.

NANCY LYNN: So as everyone can tell, we're huge, huge proponents of being involved in clinical studies and clinical trials. And that too is a difficult landscape to navigate. So I just want to mention that we just started this week another-- a subseries of this series where we actually just walk people through clinical trials, specific trials, so that you get the sense of how you enroll? What is an entry criteria? What is informed consent? So I guess, if you haven't received information on that new series and would like to, please also just email us at reply@brightfocus.org, and we'll make sure that you get the registration links for that series. Because we do acknowledge how difficult it is to navigate the clinical trial finders. And at brightfocus.org, there is a place you can go look for a clinical trial near you that's a little easier to navigate than say, clinicaltrials.gov. But there are a lot of clinical trial finders. They're just not always that user friendly.

But I will say once again that, getting into a trial or a research study is a great way to get better information, to get informed, to get good or better care. And so we encourage that a lot. Also quickly mention that Dr. Salloway has done a lot of work with brain donations. Donating one's brain after death is incredibly helpful to research. And we actually-- you know what, Dr. Salloway, we should do a separate episode about that, the benefits that come from that. And that's another thing that we ask everybody to please consider. And then it's really hard to figure out how to do it. So if you are interested in learning about that, please email us. We have actually helped some people find a place near them where they can-- say, their mother had had this wish and she just passed away. And where can I go to have my brain donated? Because that tissue that is incredibly meaningful for researchers. And I said this to Dr. Salloway. We have only two minutes left. I just want to ask you one more question that was submitted in advance because it made me smile. And so, Suzanne from Congress, Arizona wrote, is line dancing good for staving off dementia? Is line dancing good for staving off dementia?

DR. STEPHEN SALLOWAY: Well I facetiously said, depends how good a

line dancer you are. Staying active is good. So I would call line dancing being active. So yes, we all need to stay active, engaged—

NANCY LYNN: Socially engaged, yeah.

DR. STEPHEN SALLOWAY: Emotionally, socially, every way, stimulated-- it's good for our health and our well-being. And so, yes, and the physical component is really important. Walking, finding some other way to stay really physically active, and every other dimension. Dancing is certainly a good one.

NANCY LYNN: And line dancing sounds a lot more fun than my treadmill.

DR. STEPHEN SALLOWAY: Line dancing sounds like fun.

NANCY LYNN: I can't believe already are at—

DR. STEPHEN SALLOWAY: Hour's gone already.

NANCY LYNN: 59 past the hour, so we will ask you to come back. So if your question was not answered today or if you wanted to ask us about some of the other things that I mentioned, you can reach us at reply@brightfocus.org. Our next episodes on August 1-- we'll have the next one that's about clinical trials, specifically. We haven't selected which ones yet. But after this episode, I'm inclined to maybe try to find something where that you can participate in if you're APOE4-positive. And you can watch the past episodes at brightfocus.org/ZoomIn and on YouTube. And I'll also quickly mention that the field does hope that the new potential disease-modifying therapy donanemab will be approved within the next couple of months, we hope. And when that is approved, we will have an episode specifically about donanemab. Dr. Salloway, thank you so much again for your candor. And it's great to see your excitement about the future of the field, which is new for us that have been doing this for a long time. It was really a lot of not progress or seeming not progress for a long time, which always, in science, leads to progress. You have to find out what doesn't work before-- at the same time as you're finding out what does work. But thank you for donating your time today. It's deeply appreciated. And I hope you'll come back and talk about brain donations.

DR. STEPHEN SALLOWAY: Well, thank you for having me. And thanks, everyone, for joining in. And I can tell you the only reason we're at this moment of progress is because of all the contribution from thousands of research volunteers who put themselves on the line to make this possible. So I want to thank all of you who have contributed or might contribute in the future.

NANCY LYNN: That's a beautiful way to end. Thank you, Dr. Salloway, and thank you all for attending, and we hope we see you on the next one. Take care.

Resources

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

- Alzheimer's Prevention Registries:
  - https://www.butler.org/memory/registry
  - https://www.endalznow.org/
- Clinical Trial Resources and Trial Finder:
  - https://www.brightfocus.org/clinical-trials