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

New Alzheimer's Drugs: What To Expect Over The Next 3 Years
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Transcript of Zoom with Reisa Sperling, MD, Professor of Neurology, Harvard Medical School; Director, Center for Alzheimer Research and Treatment at Brigham and Women's Hospital and Massachusetts General Hospital

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

PHYLLIS FERRELL: Hi everybody! Welcome to the seventh episode of Zoom in on Dementia & Alzheimer's. I have been able to watch these, but now I have the distinct pleasure of being your host. So, today's program is called "New Alzheimer's Drugs: What to Expect Over the Next 3 Years." We're very excited today about this informational program. It's supported in part by educational grants from Lilly and Genentech. And my name is Phyllis Farrell, and I'm filling in today for the amazing Nancy Lynn, who's normally your moderator from BrightFocus Foundation. So BrightFocus is a not for profit that's been funding innovative research all over the world for the last 50 years, for Alzheimer's disease, macular degeneration and glaucoma. And we've collaborated for more than a decade and I'm thrilled to be joining you today. It's fun to be on this side. But what's even more fun is the guest that I get to introduce to you today.

Now, the best part. I'm so happy to be able to introduce you to today's expert guest. Her name is Dr. Reisa Sperling, and she's a neurologist that's focused on the detection and treatment of Alzheimer's disease at the

earliest possible stage, and she'll be able to talk with you about that a little bit. She's a professor of neurology at Harvard Medical School, and Director of the Center for Alzheimer's Research and Treatment at Brigham and Women's Hospital and Mass. Gen. Hospital. Dr. Sperling is the co-principal investigator of the Harvard Aging Brain Study and the Alzheimer's Clinical Trial Consortium. Dr. Sperling also chaired the 2011 National Institute on Aging workgroup that developed the guidelines for the study "Preclinical Alzheimer's disease" so I know she'll share that with you today. And she co-led several large studies: A4, the LEARN studies, and she's currently co-leading AHEAD 3-45. She's very, very rewarded in her work. We've seen her receive the 2015 Potamkin Prize from the American Academy of Neurology. She received a Lifetime Achievement Award from CTAD, which is one of Alzheimer's largest clinical trials, and was elected to the National Academy of Medicine in 2021. But the most important thing for me is that I get to call her friend, and I think you'll find today that while she's this world renowned thought leader, you're going to feel like you're just hanging out with her in your living room. So Dr. Sperling, so so happy to have you with us today.

DR. REISA SPERLING: Oh, thank you so much, Phyllis, and thanks to all of you guys, I'm scrolling through my screens, and I can see all of you in your great home settings, and I really appreciate people taking the time out of their day to hear more about Alzheimer's disease. And I'm looking so forward to your questions because it's you folks who are going to help us get to the end game of one day having a world without Alzheimer's disease. I'm so grateful that you guys would join us. And I look forward to talking with Phyllis especially, as she said, we've actually been friends for well over a decade, and there's a great slide of the women against Alzheimer's disease when we were starting A4 that reminds me every day of why this is so important. So have at it, ask away.

PHYLLIS FERRELL: Well, so Reisa you and I, obviously, this is a personal and professional battle for us, and I know that a lot of people on here as well have lived with this disease in their families in the past or currently, or they're worried about in the future. One of the things that I find to be really helpful is to start the conversation with talking about the disease across its spectrum of stages, and I'm wondering if you might start with just kind of a lay of the land for the folks that we have here. How do you

define Alzheimer's disease? What are the different stages? And what's the nomenclature now that we really should be using?

DR. REISA SPERLING: Absolutely so, first Phyllis, as you said, I just want to acknowledge that I've seen Alzheimer's disease up close and personal in my grandfather and my father, and so I know what many of you have experienced or are experiencing. And I want you to know that even though I'm going to talk about this from a research point of view, and also a clinical care, that I don't forget the human side of this. So Alzheimer's disease, as we now recognize it, is really a process that begins in the brain, and I'm sure we'll talk more about this, but it involves the buildup of these abnormal proteins. I'm sure you've heard by now, probably about amyloid plaques and tau tangles, and we'll talk more about that. But that begins in the brain many years, maybe 2 decades before we get to the terrible stage of Alzheimer's disease, which is what we call the dementia stage. Now, I want to start off by saying dementia, because people always ask, "Is dementia the same as Alzheimer's disease?" And dementia is a clinical syndrome, which unfortunately means people are losing their ability to do things in daily life independently. And that is progressive over time. And Alzheimer's disease accounts for about 70% of dementia in older people. So it's the main cause, but it's not the only cause. And we, especially in people who are over the age of 80 or 85, we realize that lots of different processes work together to result in dementia. But one of the really important things that's happened in the past couple of decades is, we realize that dementia is a rather late stage of a process that began earlier. So you've heard about dementia, and we generally refer to that as mild, moderate, and severe stages of dementia. But about 5 years—or even before—mild dementia, most people go through what's called mild cognitive impairment. And this is when people are still independently functioning, but things are not going quite right. They need more help in remembering things, even though they are living independently, and they notice, most importantly, changes from their prior ability to think, remember, and do things. And now we recognize that about 10 years before that stage of MCI, or mild cognitive impairment, there's a stage we call preclinical or asymptomatic Alzheimer's disease. Where again, the changes in the brain are happening. People notice very subtle changes,

and we can talk about that, but they don't yet have impairment. And the good news is that now we have ways that we can detect these changes in the brain before people have symptoms, when they have early symptoms, and excitingly have something to offer them in terms of disease modifying treatments.

PHYLLIS FERRELL: Oh, so helpful! You know, Reisa, one of the things that I love first of all, starting off with just the difference between Alzheimer's and dementia. And in Europe, they just use the word dementia for everything. In the US, we tend to say Alzheimer's for everything. And sometimes I explain it that you know, when you go to get one of these, what do you usually say? I'm going to go get a Kleenex.

DR. REISA SPERLING: I would call it a tissue, but it could be a Kleenex.

PHYLLIS FERRELL: Yeah, let's say you go get a Kleenex. Well, Kleenex is just one type of tissue. And I think that sometimes you know a good way to explain that dementia is to your point, it's the symptomatic phase and it could be caused by a lot of different things. So I'm wondering, because one of the questions that we got, actually a whole slew of questions we got, is what causes Alzheimer's disease, and if we don't really know what causes it, how can we actually be studying drugs? And so, you mentioned a little bit about amyloid and the buildup in the brain, and so talk a little bit about maybe what these different causes could be and what is Alzheimer's specifically please.

DR. REISA SPERLING: Absolutely. So, Alzheimer's disease is defined again as changes in the brain due to this accumulation of abnormal proteins, and that the nerve cells that are in the brain begin to show changes and damage. I will say that even though I work in amyloid land and I'm so thrilled about new treatments and new diagnosis, I think amyloid buildup is part of the picture, but it's not everything. And that's important as we talk about the current medications and what's coming in the future. But amyloid is this protein that we all make in our brains. Actually, all of our nerve cells make it as they're active. And unfortunately, as we get older, we seem not to be able to handle that protein as well as when we're younger. There's a famous neuroscientist who's now at the Brigham who talks about emptying the protein garbage. Now, that may not sound very

beautiful, but that is what our brains need to do. Our nerve cells make these proteins, and we need to get rid of them; empty the garbage. And one of the first ones that we have trouble emptying is this buildup called amyloid. And you've probably heard of these plaques, and people think of plaques on their teeth, plaques in their heart arteries. Amyloid plaques in the brain are a little bit different, but they do build up outside these nerve cells. And we've learned recently that that buildup may be very important to clear, to help the brain get rid of, so that the nerve cells can talk more easily to each other. The other thing you'll hear me talk about is something called tau. These are what cause tangles, if you've heard about those in the brain, those are inside the nerve cells. And I'll say we don't fully understand how the amyloid plaques and the tau tangles interact. But we know that they do interact. And we also know now that by changing amyloid early enough, we may be able to slow the decline, at least change the way the nerve cells are reacting. And that I would say it's taken us a quarter of a century to definitively prove that since I've been working in Alzheimer's disease, and it's really thrilling to see that evidence. But it's part of the story, and of course, what we all want is to completely prevent decline one day, and that may take more than amyloid alone, or it may take going even earlier in the disease.

PHYLLIS FERRELL: Reisa, I've worked with you for 15 years and I swear every time I talk to you, I still learn something. So we've got amyloid plaque outside the cells, and then the tau tangles inside. So that amyloid and tau are those two pathologies that define Alzheimer's disease. But something happened about 10 years ago, where it used to be that we couldn't actually see those things until a brain biopsy or an autopsy. And a lot of you know people they're living don't volunteer for brain biopsy. So how do you find out if people have this amyloid and tau and how's that really changed the research and the future that got us to where we are today?

DR. REISA SPERLING: Absolutely. So, you probably heard the term biomarker or imaging. And what's really thrilling is that we can see evidence of this protein build up during life. And, as Phyllis just said, you know when I started medical school, the only way to make a diagnosis of Alzheimer's disease was after someone passed, and or getting a very

rare brain biopsy. And it's actually almost been 20 years now since the first amyloid PET scan where we could see evidence of these amyloid plaque buildup in the brain using a PET scan. And that still today is being used. It was used in a lot of these clinical trials to define someone as having Alzheimer's disease if they had mild cognitive impairment or mild dementia, this PET scan to see evidence of amyloid plaques. You can also see tau with a different kind of PET. And that's part of the reason we can see the amyloid and the tau working together, unfortunately to result in memory problems and dementia. And then we also have, you can see, these proteins in fluid. So one way is cerebral spinal fluid. You've probably heard about this. It sounds scary, but I've had to a spinal tap or lumbar puncture, and that's very helpful for research. But of course many people are not knocking at the door to have lumbar puncture done.

We've now figured out how to measure these proteins in blood. They're not perfect yet, these blood tests, but they're getting much better, and they're pretty good at telling us what someone's PET scan would look like. So you'll hear more about this, I'm sure, over the next year or two, but I envision that these blood tests will allow us to help make a diagnosis with your doctor if you have symptoms, and ultimately, perhaps in future studies even before symptoms to help us know who's got these changes going on in their brain again hopefully, as early as possible to start treatment.

PHYLLIS FERRELL: I'm going to ask you one more question about kind of the basic science. I know everybody really wants to get into some of these therapies. But you know, having been at this not as long as you, but for quite a while, I've seen all these headlines and all this stuff about failure, failure, failure, failure. And of course, I get really frustrated because I know that no negative study is actually a failure unless you don't learn from it. But one of the things that used to be a battle is amyloid versus tau, amyloid versus tau. In fact, I remember an article you were quoted in, probably 8 or 9 years ago, where you talked about the Baptists and the Taoists, and that in fact, maybe these are actually part of the same disease cascade. So, you know, sometimes in the literature, in the earned media, it's seems to be pretty disconnected from the science, and I'm still hearing some of these battles about amyloid hypothesis and amyloid versus tau. And I think is someone who might think about taking one of these medicines or encouraging my mom to take one of these medicines,

having confidence in where we are in the science is really important. So, could you clear up some of this for us about amyloid versus tau and the amyloid hypothesis? And what do you think we know right now? And maybe what we don't know, which is obviously also is important.

DR. REISA SPERLING: Terrific question Phyllis. So, what we do know is that in people who have cognitive impairment or dementia due to Alzheimer's disease, they have both amyloid and tau. If you have just tau without amyloid, first of all, you don't usually have impairment, and if you do it's not Alzheimer's disease. There are other dementias that have just tau. Amyloid probably starts to build up and wide spread in the brain before the tau was widespread in the brain but they do go together. And we can see that at a certain level of amyloid the tau seems to be spreading unfortunately, like a forest fire, I often use that analogy. So, we don't yet know for sure whether amyloid causes the tau, or whether something that's behind both of them with our problems with protein. But we should stop fighting about whether it's amyloid or tau. We should try to work on both of them. And I'm thrilled because our next clinical trial, funded by the NIH, will look at combination therapies looking at amyloid and tau, because once you already have symptoms, as I said, you have both amyloid and tau, and we may need both to really affect treatment. But again, I think amyloid is a key part of the puzzle. And these treatments that we'll talk about or going after amyloid. But it's not the only thing, especially once people have significant memory problems. So, we're going to need more than just amyloid. We're going to have to go after tau. And also, I saw Dr. Jenny Rabin on here who I know works on vascular disease. And I think that's an important piece too, that we need to try to keep our brains healthy and resilient and prevent stroke or other things that can contribute. Just like heart disease, cancer, diabetes, all of these diseases going early has been helpful, but also trying multiple different mechanisms to try to, especially once people already have significant damage, and I think Alzheimer's disease will be the same.

PHYLLIS FERRELL: I couldn't agree more, and I want to get into this idea of why is it important to know what might be causing the cognitive impairment? But before we do that, since we kind of tickled a little bit at this, and what new therapies are out here? So a lot of excitement

about Leqembi and another drug that's under review by the FDA right now called donanemab. They're called disease modifying therapies. As you mentioned they target amyloid. Talk a little bit about what these medicines are, what they do, and why are they different from the things that we have today?

DR. REISA SPERLING: Absolutely so both lecanemab, which as Phyllis said, has now been FDA approved, called Leqembi, and donanemab, which is under consideration. Both of these are what we call antibodies that are targeting these amyloid, not just the plaques, but different forms of amyloid in the brain. And you may not know, cause I certainly didn't know, what is an antibody? So an antibody is something our body usually makes to try to go after proteins or invaders. So we have antibodies. That's what when you get a vaccine against measles, you make antibodies. When you have exposure to COVID or something else, your body makes antibodies. The brain though is kind of a special place, and the antibodies that we make overall in our body, only some of them get into the brain. And what we figured out, again almost 20 years ago now, is that using the immune system, the innate immune system, that helps the brain clear proteins, that we could do that by giving antibodies that are targeted against the amyloid plaques and other forms of amyloid. So basically, these antibodies which are now given by IV infusion, but I suspect very soon, and we saw some very exciting data about that at CTAD, will be able to be given by an injection hopefully at home with people by themselves. But these antibodies help the brain activate the cells that are important for clearing these proteins, and in particular for clearing amyloid.

Now, we've been working at this actually since the year 2000 and people often ask me, well, why did it take us a quarter of a century or so to succeed? And there are multiple pieces of that. But I'll tell you my opinion on this one. We learned that we have to go earlier. So these current trials that are disease modifying and the first approval, were in people who have mild cognitive impairment or very mild dementia. And we even see within those trials that the people who responded best were at the earliest stages of symptomatic disease and at relatively lower amounts of amyloid. So I think we've gained a lot by moving backwards in this trajectory by 5 or 7 years since the first trials. Secondly, we learned that we have to be aggressive. Alzheimer's disease is a formidable opponent,

and we have to be serious about dosing these antibodies at a level that's high enough to really activate the brain and really knock down amyloid quickly. That which we should talk about. Part of the reason that took a while to happen is that in a small percentage of people, that removal of amyloid is associated with changes in the blood vessels in the brain. So I'm sure you've heard about the concerns about bleeding or swelling. We call this ARIA, amyloid related imaging abnormalities. I was accused of calling it something beautiful, when of course, it's a side effect we want to avoid. But the good news is, I think we've learned a lot about who's at greatest risk for developing this side effect, and how better to manage it. But that is what part of the reason it took us a long time, because you want to dose high enough to remove the amyloid but safely so that you minimize the side effects associated with these antibodies. And then I think the other thing that we're realizing again is that it's not only removing the amyloid, it's moving enough amyloid that people are getting back down to what we call close to amyloid "negative". And I put that negative in quotes, as I'm not really sure we completely eliminate amyloid. But we are realizing we have to get it down to a level that people's brains can catch up on clearing out not only the amyloid but potentially other proteins by really knocking down the amyloid. I hope that was an okay explanation.

PHYLLIS FERRELL: No, it's a great explanation. I actually want to get into kind of some of the future of where the research is going as well. But I think it's important to ask just a couple more questions about these therapies that are available now. So we heard earlier is better. Now we're talking about in the symptomatic phase, right? So as soon as something is going on in your brain that's different than what you expect, talk to your doctor. Sometimes I give conversation, I talk to women's groups, and I say, if you found a lump in your breast, and you told the doctor, and the doctor said, "Well, let's give it a year and see what happens", you know you'd go find another doctor right? So you know best your brain. And so this idea of earlier is better. I also heard accurate is really important. This idea of a differential diagnosis. And I'm assuming that's because these therapies right now have some very specific things about inclusion criteria, like who would be eligible for them? Is that something you can talk about, at least in generalities across the class?

DR. REISA SPERLING: Absolutely. Because I think you're absolutely right, Phyllis. Those two aspects are really what I think has helped us get to this successful point so far. So again, the trials were done in people who had mild cognitive impairment or very mild dementia, so at a pretty early stage of symptomatic disease. And that is the current approval and both by the FDA and what is generally covered right now by Medicare with a registry process. We do need evidence that people have amyloid build up in their brain. That is required right now for coverage. And right now that is primarily PET scans and spinal fluid, although there is the option now for other, and again, these blood tests, I think, are important cause that would make it much easier for many people to get an accurate diagnosis that Alzheimer's disease is contributing to their impairment quickly as possible. But I do think it's important that if you have symptoms, it's worth talking to your doctor as soon as you can. I'm acutely aware that we don't have enough specialists in this. We don't have enough PET scanners in this country. There are many people, particularly from underserved communities, who are not able to access a tertiary specialist, meaning a super specialist in an academic medical center. And we need to find a way to make this easier for primary care doctors, for geriatric doctors to make this diagnosis and initiate treatment. So I do know that right now is a difficult time, because we have this exciting potential therapy. But we need to figure out how we can get it to people who are most likely to benefit.

And I do want to talk about that for a moment, because there are people who should not get these therapies right now. And that I have to say, as a neurologist who takes care of patients, one of the hardest things is when someone has been waiting patiently in my clinic for years to get a disease modifying therapy, and unfortunately they have a criteria we'll call exclusion criteria that means it's either not safe for them to get it if they have evidence of a lot of prior bleeding in their brain, we call them micro hemorrhages if you talk to your doctors about this, or that they've advanced to a stage of disease where this particular therapy is less likely to help them. People in moderate or severe dementia stages. And I have to say that is heartbreaking I'm sure for my patients and for me as a doctor. But I think we have to go with the evidence, and the evidence so far suggests that there is a fairly narrow slice at the early stage of

symptomatic disease with people who have amyloid build up for whom these drugs did slow decline. And that's a start. And we will figure out how we can extend the indications in the future with again, combination therapies or going to asymptomatic people. But right now that's where we are. And so I do think it's important for people to realize that not everybody who goes to their doctor will be able to get these medicines. And again, that's heartbreaking for your doctors as well as for you. But we have to follow the scientific evidence and do what we can to help people.

PHYLLIS FERRELL: Yeah, and one more question about these therapeutics. Because I think this, you mentioned it briefly, that earlier was better in how they performed as well. So part of it is, you know, catching it early enough so that they're an option for you or your loved one, but also that it works a little bit better. But how can I tell this is working and based on the evidence how much is it working like? What should we expect, at least based on the trials?

DR. REISA SPERLING: I think that's an excellent question. And you use the term earlier Phyllis called disease modifying therapy, and I'll say that we've made the distinction for a long time about symptomatic drugs and disease modifying therapies, and it's worth just understanding what I think people mean by that. So right, we've had FDA approved medications for the symptoms of Alzheimer's disease for a long time. Drugs like Donepezil or Aricept, or several other drugs that are working on chemicals in the brain that nerve cells use to talk to each other. We call them neurotransmitters. Those I consider symptomatic drugs because they do help people thinking in memory a little bit, but they don't slow the underlying process in the brain. They don't slow the disease progression. This new class of drugs, these antibodies again right now lecanemab being the first approved, they go after the underlying process in the disease, but they may not show evidence of symptomatic improvement because they're slowing future decline. I hope that the combination of the two together, and most of the people in the clinical trials were on symptomatic medicines when they started the disease modifying. But I think it's important to realize that a disease modifying drug, at least at the stage we're currently giving it for most people is going to slow future decline, and it probably will not make

people better from where they are now.

Now, I will say there's some glimmer of hope that in the earliest, earliest people maybe there's a hint that we can make people a little bit better, but mostly we can stabilize them or slow the decline. And people say, well is that clinically meaningful. You know, I realize that's a nuanced debate about what is clinically meaningful. And this is a personal thing, but so far it looks like we can slow the progression by about 5 months in an 18-month trial. So it's about 30% slowing, or between 25 and 35% depending on which measure you use. And of course, I want 100% slowly. This is what we're aiming for to see if we go earlier and testing and the AHEAD study and other prevention trials. But for many people keeping them at that independent stage where they have very mild impairment or MCI for an extra 5 or 6 months is meaningful to them, and that is what, of course, led to I think the approval and Medicare coverage. So we have to be realistic that these aren't wonder drugs. We're again not going to suddenly get a memory we had when we were 25. We are only slowing a process that's still continuing. And we're not at 100% slowing yet. But it's a start. I like to use the baseball analogy, we haven't hit a home run, but we've hit a solid double. We've got women on base. And that's how we start and we will do better over time.

PHYLLIS FERRELL: Yeah, I love that analogy I've heard, "Are we at the beginning of the end or the end of the beginning?" But I don't care. We've turned a corner, so I am going to pull that thread that you just mentioned. We've talked now about kind of the drugs that are available today in the symptomatic phase. You've mentioned earlier is better. And make sure it's accurate, your diagnosis is accurate because it can help you and your doctor determine what's the best course of action for you. But I know what you're really excited about, and I know what you and I've been working on for over a decade. So what's coming next when we really talk about where we could go with this science recognizing, we're still in the research phase.

DR. REISA SPERLING: Absolutely. So I admit to huge bias here, because I've been working on treating people before they have symptoms for more than a decade. But I think all of the evidence in the current trials, as well as other evidence, is that again the amyloid build up begins 20 years before dementia, and that our best chance to bend the curve is

going earlier. And now we have this ability to see the amyloid buildup before there are symptoms with PET scans and with blood tests now. I am working on a study that is what we call a public private partnership study. It has NIH funding and partnership with a company where we're testing lecanemab, the first FDA approved medication in people who don't yet have symptoms, who are 55 to 80. And it is a trial, it's a what we call a placebo-controlled trial. So you don't know, I don't know who is on medication, but we're trying to see if we started earlier, and these people are probably 5 to 10 years earlier than the current trials where lecanemab and donanemab were tested. We're hoping that by starting at that stage we might be able to get even more cognitive slowing, and we have to test that. But for that, of course, we need people like you and your friends and your neighbors, because the only way we will get answers in these trials is people who are willing to dedicate their time and volunteer for these studies. And I know firsthand how hard that is on people and their families, but it is the way we will get answers. So I'm excited to be working on this. And I'll also say, as I mentioned, there are multiple other trials. So even if you do already have symptoms, there are many opportunities for research, for trials. There's pretty much a trial for almost anyone who wants to be in a trial, and if you are at a more advanced stage of disease or your loved one is, there are trials working on late-stage symptoms, on behavioral symptoms. There are trials working on the combination of factors. As I mentioned, we will start an amyloid and a tau trial. I just want to encourage you to say, look we think we're on the right path, but we can do even better. And the way we're going to do that is by having people being willing to come into clinical trials and go on this adventure with us.

There were a couple of specific questions, Phyllis, I saw in the chat one that someone wanted to go back to safety. And I do want to bring that up, because it certainly comes up, especially when you go even earlier in the disease, where people don't yet have impairment, and these drugs do have risks. So one, we hope also, by going earlier that we may be able to decrease some of the risks of the brain swelling or bleeding because there's less amyloid in the brain. So that's number one. Number two, we also are trying ways to dose it, what we call titrating. If you've ever heard that term when we start with a lower dose and then move up trying to decrease the risk.

The question about APOE4 carriers is important. So APOE4, I know there's been a wonderful BrightFocus seminar before on genetics which you can see, but APOE4 is the most common risk factor for older people who develop Alzheimer's disease. It's a complex gene. It doesn't mean all E4 carriers will get Alzheimer's disease, and many people with Alzheimer's disease, 40% don't carry an APOE4. But it APOE4 does seem to change the likelihood that amyloid lowering drugs will have an adverse effect. So we have to watch people who are E4 carriers very carefully.

One of the questions in the chat was about can people be on blood thinners? And I'll say this is still under investigation. But the recent data that came out suggest that the increased risk is pretty small for people on blood thinners. And in some studies it's not an increased risk. This is something you should absolutely discuss in great detail with your own doctor, because for every person it's a risk benefit ratio. And so in our trials we can be super careful about, you know, monitoring people like a hawk with our scans and watching them closely. When this is in the clinic, this is the decision you need to make with your doctor about whether it's the right treatment for you, especially if you're on a blood thinner.

PHYLLIS FERRELL: Reisa, I'm looking at some of the questions that came in earlier, and you hit them already. Some of these things around APOE4. And how do these drugs work differently? And in some of these populations. But one that did come in that you didn't mention is, do we know if this works different between men and women or people of color or not? Do we know anything about these drugs in kind of some of the sub populations that are that would be in the studies?

DR. REISA SPERLING: Really good questions. So I would say overall that between men and women they work similarly. But we are not, this is a technical term, we are not fully powered to say, is there a difference between men and women. So overall there are more women in these trials, because more with women are affected, and with late stage or later life, I should say, Alzheimer's disease than men, and there was at least some analyses that said, maybe women didn't do as well. But women, there's an interaction between women and APOE4. That needs to be explored. Women who have APOE4 alleles are at risk for faster decline.

More tau, which is a really interesting thing that we need to understand. But overall, I would say that men and women respond similarly.

The question about underrepresented populations, minority populations, is critically important. So most of our trials, despite working pretty hard, have not succeeded in enrolling a fully represented representative population. So I would say, we are definitely not, we don't have enough people to fully understand whether they work differently or not. Having said that, there's no evidence so far that people who come from communities of color, in particular, black or African Americans, Latino or Hispanics, or Asians respond less well. In fact, in one analysis they responded better for a given amount of amyloid. But we also know in communities of color more than amyloid is contributing. So there are higher rates of vascular disease that might contribute. We see lower levels of amyloid markers in some populations. So this is such a critical area of research. And part of our job is to do a better job of partnering with these communities so we can really get answers and develop treatments that work best for everybody. And I would say, that's the challenge of the next 5 to 10 years especially.

PHYLLIS FERRELL: I want to talk a little bit about how we can all help advance your research. And this idea of clinical trial participation. But I did have one other question that I wanted to ask you. We talked earlier about how important a differential diagnosis was right. And is your dementia Alzheimer's or is it vascular dementia or FTD? And I did have a question come in advance that says, "Are we just doing all of our research in Alzheimer's? And what about Lewy body dementia and FTD? And does the Alzheimer's research help those other things?" And so thoughts that you might have for folks that may already have a differential diagnosis or had a family member that had a dementia diagnosis that wasn't Alzheimer's.

DR. REISA SPERLING: Absolutely. So, two things, one is these biomarkers we are talking about for amyloid are really making a difference in making an accurate diagnosis. Because sometimes people are told they have Lewy body dementia. I have told the patient I thought they had Lewy body dementia because they had that constellation of symptoms. And when they got these biomarkers, they may have had Lewy bodies, but

they definitely had some Alzheimer's disease pathology contributing. So that's number one, is we have good biomarkers for Alzheimer's disease. We don't yet have perfect biomarkers for Lewy body and for what's called frontotemporal dementia. So I think we're working on those. They're getting better. But we can at least know whether there's Alzheimer's disease contributing with these biomarkers. And I think we'll see more of that.

Absolutely the research in Alzheimer's disease is helping. I believe research in Lewy body and frontotemporal dementia because both of those dementia diseases involve the buildup of proteins, different proteins. You might have heard the term alpha synuclein or progranulin, or again tau, in some forms of frontotemporal dementia. But these build up in the brain in a way that's like Alzheimer's disease, and that we are have these proteins that accumulate in cells like tangles but they're different. So everything we learn about how do we help the brain clear proteins, I hope will help these other diseases that people can have. And secondly, the funding that's come through the NIH and other philanthropic partners for Alzheimer's disease, says Alzheimer's disease and related dementias, or Alzheimer's disease and related disorders. So one of the really important things is we've also seen important funding in these other diseases as well. Because, again, as a neurologist who takes care of patients with many disorders, we need to fix all of them, not just Alzheimer's disease.

PHYLLIS FERRELL: Well you mentioned some of the symptomatic therapies that were being studied, too. I think there was a new one approved for aggression and agitation, and some of those could be used potentially regardless of the other underlying pathology. Not all of them, but some of them could as well. So maybe just the fact that we're having this conversation around Alzheimer's disease can help benefit all of the research.

DR. REISA SPERLING: Absolutely, and in fact, some of the symptomatic medications are used in mixed dementia, vascular and Alzheimer's and Lewy body, although the side effect profile might be different. I didn't say enough about vascular only because that is something you can do, all of us right now, as we do this. Which is keeping our brains as resilient as

possible to whatever disease might be coming as we get older is key. And so controlling blood pressure, exercise, sleep. All of these things that are important, and particularly for...we can see that vascular disease interacts with Alzheimer's disease and hastens cognitive impairment and increases those tau tangles. And that is something we can all do, which and I know this is "Do what I say, not what I do", because I'm still sitting here in my chair, instead of being out there walking and doing things. But I'm very convinced. I don't think that exercise will fix Alzheimer's disease, but I think it will make your brain more resilient if Alzheimer's disease is in your future because of parents or other influences. And so that's something we can all do is make sure our blood pressure is good, we sleep enough, and especially get out there and exercise.

PHYLLIS FERRELL: I love that advice, and often I talk to working moms and say you need to start doing this in your forties. Don't laugh at me when I say, "You need to get some rest, leave the dirty dishes in the sink and go to bed." And so I think, giving ourselves some permission. So I want to come back to how we can help you with your research. I have done a lot of clinical trials, as you know, and you mentioned how hard it was to tell someone that they might not be eligible for a new drug. I've had to go through this situation where I had a friend say that there was something wrong with their mom or dad. Can I refer him to a neurologist? I tell him where to go? And then they call me, and they say my mom and dad is too far advanced for this study. And that's heart wrenching to me, too, because I feel like we took their choice away from being in research. And this is someone you know, someone who wanted to participate in research. I was trying to get research done. And so how can we help you if someone wants to participate and a symptomatic trial, a pre symptomatic trial. Maybe there's a trial that's around cognitive behavioral therapy, or there's a large observational study going on. There's studies going on diet and exercise. So there's all types of studies. How does one help you? Because we love you Reisa. And how can we help in general? Answer both questions.

DR. REISA SPERLING: Okay, so at least for the trial I'm working on, AHEAD study, I saw already the aheadstudy.org. You can click on there. There's 70 centers in the United States and hopefully one near you, and you can

see if you're likely to qualify. The first step in that one is a blood test to say, are you or not more likely to have amyloid built up in your brain. But there are multiple studies going on. Some that are NIH sponsored. I work at the Alzheimer Clinical Trials Consortium, which is running 3 trials now at the beginning, middle, and unfortunately end stage of disease with people who are already in hospice. So there's opportunities there. The clinicaltrials.gov, which I saw link to that here I have to say that's hard even for a person who does clinical trials to find a study on there, because it's in kind of fancy language. But you can look there and search under Alzheimer's disease and see some. The Alzheimer's Association also runs something called TrialMatch where you can go there. And your local, often I actually find local chapters of the Alzheimer's Association, especially for people who are symptomatic, helpful because they know what trials are going on in that area. And again, if you already have symptoms, it's important to get into a trial soon and ideally, one that's convenient for you, that's nearby that you don't have to travel. And so I think local chapters are great.

I do think we have to do a better job at getting resources out there. So it's not hard for people to find. This is something I really want to work on. But there are ways now that you can look, and there'll be more in the future. The AHEAD study, I think, is only one of many studies that will be targeting people helping to try to treat as early as possible. And there already are studies of diet and exercise, the POINTER study which is going on, although I think they may be close to finishing enrollment, if not, which is a diet and exercise study. But there will be more. And I think if you want to be in a study, it's our Center's job to help find a study who's right for you. But you do have to go in with the mindset that not every study is the right fit for every person, either for safety reasons, or for the likelihood of benefit. And it's our job to try to find the best study for you and for the studies to find the right fit for them. That's the tough thing about research.

PHYLLIS FERRELL: Yeah. And a big thank you to Sharyn and the BrightFocus team because they are capturing these resources in the chat. I think another one I would mention is the Banner Alzheimer's Institute. They have a registry there that you can sign up for. And the nice thing about that registry is clinical trial sponsors then can advertise through that

registry. So if you've signed up and said, let me know, which is a little bit about how Alzheimer's Association clinical TrialMatch is as well. You put your information in there. You might not see the right trial for you right now, but 6 weeks from now a sponsor may see you, and then, you know, they'll reach out to you.

DR. REISA SPERLING: I'm so thrilled you mentioned the Alzheimer Prevention Initiative. And I'm going to mention one more because we're increasingly going into how do we reach people all around the world without making them come into a center? So there's something called the Alzheimer Prevention Trial, which is a website APT Webstudy. I don't know if you've got that.

PHYLLIS FERRELL: I wondered when you were going to mention that.

DR. REISA SPERLING: Well, and the reason I'm so excited about that one is we have a new piece of that called AlzMatch, where we send people, they can go to their own Quest, to their own local blood center and get a blood test as part of that new initiative. It's just starting, but this is, of course, what we need to do to be able to find the hundreds of thousands of people who might be at risk and see if they're interested in coming into trials. So I think there'll be lots of these initiatives and these registries. The good news is, we all work together also. If we have a trial that we know people on the Alzheimer Prevention Initiative might be interested. We work with them and vice versa. Because we have to all be in this together.

PHYLLIS FERRELL: Yeah, BrightFocus has really taken a leadership role here too, on making sure, people are matched and reaching out to those areas of the country that might not often get the request to participate in a clinical trial, communities of color and rural communities. So super thankful for them. I know we're really short on time with you Reisa. I'm going to ask you one more question. What we're hearing from you is earlier is better, accurate is important, research participation is key. And let's have a big sense of urgency around this. So I get to ask you one more question, and that is what gives you hope about where we are? You and I have had lots of conversations about our daddies, and we've changed our careers because of our family. So you're sitting here at the end of 2023. What gives you hope?

DR. REISA SPERLING: Well, it gives me great hope that we've made progress enough to have something to offer to at least some people who are suffering from this disease. So that's incredible. It gives me great hope that we have ways of detecting Alzheimer's disease much earlier, because that is how we've really made strides in cancer and heart disease and diabetes. It's detecting disease before you come into your doctor. And so those trials, like the AHEAD study and other trials, I think, give me great hope that if we started soon enough we could really have an impact. The other thing that really gives me hope is the people on this call, and the people I get to work with. There are so many people focused and dedicated to Alzheimer's disease now, and that was not the case 25 years ago. Everyone thought, there's nothing you can do about it. Why should we spend time and money on this. And these successes tell me, you know these glimmers of successive has already changed our field, and I expect incredible things. And I always like to say, at least for our families, Phyllis, that my greatest hope is that our kids, and especially my grandkids, they're not going to be afraid of Alzheimer's disease in the way we are, because it will be a treatable and hopefully preventable disease in the time I have grandkids. So that's gives me great hope, and it's an honor to be able to be part of it.

PHYLLIS FERRELL: Well, Dr. Sperling, what gives us hope is that you are so persistent. I know that when Reisa called, I should just say yes, because I was going to get there, anyway. And having researchers like you that are committed to this field is really what gives me hope. So thank you. I know you are off to some research activities right now, and we just want to thank you for sharing your time with us.

DR. REISA SPERLING: Oh, thank you. Thanks to all of you, and thanks very much, Phyllis. It was a pleasure.

PHYLLIS FERRELL: So a couple of closing comments for those of you that are listening in. I know we didn't get all the questions answered. Although, Sharyn, you are a machine, not sure how you kept up on everything in the chat. If you did not get your question answered today. Please email reply@brightfocus.org. They will also be sending out a recording of this transcript by email, or you can catch up on previous episodes by visiting

brightfocus.org/zoomin. BrightFocus has a wealth of resources available all at that BrightFocus website. You can get free copies of those resources, or you can call them at 855-345-6237. And I'm sure that the BrightFocus team will roll this into the chat, too.

There is, you heard a lot about research today and how to participate. I think, I never had someone tell me they wish they'd enrolled in a clinical trial later. Every person I knew said, I wish I'd done this sooner.

There's another research opportunity that I'll bring to your attention. This one is an interview, and it's with the Center for Information and Study on Clinical Research Participation. And there's a slide that shows the information there. It'll be in the chat, I'm sure. It'll also be available on the BrightFocus website.

So as we wrap, we will be taking a short break during the month of December. Hopefully, you all are getting ready to celebrate wonderful family time and loved one time over your holidays. But we will be back next year on January 25th. And you guys are going to get to hear from another great friend of mine, Dr. Jeffrey Cummings, who is based in Las Vegas, Nevada, and I know you'll enjoy your time with him very much. So that's all from me and the BrightFocus team today. Stay tuned for more information, and I wish you all the best. Take care. Bye-bye.