

What's New in Alzheimer's Blood Testing

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

NANCY KEACH: From BrightFocus Foundation's Alzheimer's Disease Research program, I'm Nancy Keach. Welcome to the 48th episode of Zoom In on Dementia and Alzheimer's. This program is generously sponsored by Lilly, Biogen, Eisai, and Genentech. And we are very grateful to these sponsors for making these free programs possible.

Today's program is What's New in Alzheimer's Blood Testing, and I am delighted to introduce today's guest expert. I call her one of my sheroes. Dr. Suzanne Schindler is an associate professor of neurology at Washington University School of Medicine. She is a renowned clinical neurologist and neuroscientist, dedicated to advancing the diagnosis and treatment of Alzheimer's disease. Dr. Schindler cares for patients at the Washington University Memory Diagnostic Center, and she leads the fluid biomarker core of Washington University's Knight Alzheimer's Disease Research Center. And hopefully by the end of this program, we'll know what that means, fluid biomarker core. As an active educator, Dr. Schindler trains clinicians on how to integrate Alzheimer's biomarkers into their evaluation of patients with cognitive impairment. Welcome, Dr. Schindler.

DR. SUZANNE SCHINDLER: Thanks so much, Nancy. It's great to be here. And thanks to all of you for joining us today for this discussion.

NANCY KEACH: And thanks for coming. I think it's probably been over a year since you've been on the program. And there's a lot of updates, so I'm really excited to have you back. Thank you, Dr. Schindler, you sent me a great slide presentation to help me prepare for this episode. And on slide six, it jumped out at me, I read Alzheimer's disease is misdiagnosed or not diagnosed in 30% to 40% of patients. I'm going to read that again. Alzheimer's disease is misdiagnosed or not diagnosed in 30% to 40%

of patients, and then you wrote-- the bottom of the same slide-- biomarkers can determine whether Alzheimer's disease pathology is present and may be causing or contributing to cognitive impairment. So I'm going to start here. What is a biomarker?

DR. SUZANNE SCHINDLER: So that's a great question. One thing that I certainly have come to appreciate is that cognitive impairment is very common. And cognitive impairment can be caused by many different issues, not just Alzheimer's. But you can have cognitive impairment because you're taking sedating medications, because you have sleep apnea, because you've had a stroke, because you have Parkinson's disease, all kinds of different issues. And often in patients, they have multiple things going on.

And we have learned that the symptoms of Alzheimer's-- so people often think about short term memory issues-- that they're very nonspecific. And when you look at clinicians, primary care providers, or even memory specialists like me and ask us, does this person have Alzheimer's disease pathology in their brain that is causing their symptoms? We're not very accurate. We're often wrong when we make that guess. So how do we know whether this Alzheimer's disease pathology is even there.

You know in the past, people had to have an autopsy to have a definitive diagnosis. And then we got these spinal fluid tests and amyloid PET scans that let us know when people were living, still alive, whether they had these changes. Well, now we have blood tests. And so what these biomarkers do is they measure things. And this can be in our blood. This can be in spinal fluid. This can be with a brain scan. They measure things that are associated with some biological property. In this case, we're talking about this Alzheimer's disease pathology, the amyloid plaques and tau tangles.

So now, with a blood test we can tell whether someone is likely to have these brain changes or not. And that's very helpful in providing an accurate diagnosis to our patients. And some studies have shown that when we get that information from the blood test, we are much, much, much more accurate in determining whether patients have this pathology and have this pathology as the primary cause of their cognitive impairment.

NANCY KEACH: I'm going to go to Jane Haley. Go ahead, Jane.

JANE HALEY: When you say that you're using the biomarkers to help with diagnosis, how often is that followed up? Once the patient has passed on, with an autopsy to confirm it with pathology. The standard way of doing it.

DR. SUZANNE SCHINDLER: So we do this in our research studies. So that's an important question. It kind of goes to how do we validate these blood biomarkers or

other types of biomarkers are correct. And we do this in our research. There's been quite a number of studies. And some of those are what led to the FDA approval, for example, of the amyloid PET tracers. And there's more studies that have also looked at how the neuropathology corresponds to the spinal fluid tests and the blood tests. And the associations are quite high. But that's a good question.

NANCY KEACH: Yeah, and my follow up question was, what other tests besides blood tests are currently being used to diagnose? And you mentioned lumbar puncture and PET scans. And Russell from Washington, DC wrote in, "Are the blood test results alone sufficient to clearly indicate the presence or absence of Alzheimer's disease biomarkers," meaning amyloid or tau. And he says, "that is to say, is confirmation via PET scan or spinal taps still necessary to really confirm the biomarker's there?"

DR. SUZANNE SCHINDLER: So another excellent question. And there's been quite a bit of discussion about this in the clinical space. And I think the answer is-- it depends. So if you have a patient where they have an intermediate value on any of these tests, whether it's a blood test, a cerebral spinal fluid test or a PET scan, and it's kind of borderline, you need to do a second test or further evaluation. Especially if the patient is younger or the symptoms aren't necessarily completely consistent with Alzheimer's.

And so that's clearly examples of when you need to do further testing. But if you have a patient who has a very typical Alzheimer's disease, dementia syndrome, they're older even before you do any of these tests, their likelihood of having this Alzheimer's disease pathology is often around 80-85%. And in that context, when you do any one of these tests, whether it's blood, CSF, or cerebrospinal fluid, or PET, a positive result almost guarantees that they have this Alzheimer's disease pathology in their brain. So in that context, doing another test doesn't necessarily make a lot of sense.

Some people are still doing that. The issue with doing a test and then doing another test and doing another test is that it can just delay the diagnostic process and sometimes initiation of treatment. And then also you get false negatives, sometimes, that make things even more complicated. But our practice is, if it looks a lot like Alzheimer's and everything makes sense for Alzheimer's, and the test is positive-- it's Alzheimer's. Almost 100% of the time.

NANCY KEACH: Yeah. And I'll just reiterate, a blood test ultimately is going to be a lot less expensive, easier to get, ultimately, than PET scans, which are very expensive. Cerebrospinal fluid, obviously, is a little uncomfortable to get that. A lot of people are afraid of that test. And so everybody is rooting for the blood tests to be able to eliminate, to a great extent, the need for those other costly and invasive tests. And I

wanted to ask, so when you're looking for a biomarker, something in the blood here that's going to tell us this looks like it could be Alzheimer's disease or at least, this is the presence of this amyloid or this tau. What are the various biomarkers associated with Alzheimer's disease?

We have A-Beta 42, A-Beta 40, p-Tau 181. So I don't think people are really clear on what these different biomarkers are. And which are the best, how are we using them. So if you could just give a basic landscape there of what are the various biomarkers that are associated with Alzheimer's disease. And then everybody we will get into how these results get interpreted to you and the ranges and stuff like that.

DR. SUZANNE SCHINDLER: Sure so yes, there's a lot of different tests that are available right now and it can be quite confusing. So one test is the ratio of amyloid beta 42/40. And this test, the value actually goes down. So the ratio goes down as people deposit amyloid in their brain because it's the amyloid beta 42 is getting stuck in the plaques. And so the levels in the blood actually go down. It turns out that is not a great biomarker of these plaques, because we actually, in our blood, have other sources of A-Beta 40 and A-Beta 42.

And so the associations with the brain changes are not as strong with that test. There's also these levels of p-tau. So p-tau 217 is the best biomarker of Alzheimer's disease pathology. For some reason tau has changes in it. As you develop Alzheimer's disease and the levels of p-tau 17 go up, with amyloid pathology and with tau pathology, and they go up a lot. So they go up maybe 500% So it's a big change p-tau 181 also goes up, but it's not as much and not as strongly associated with this Alzheimer's disease pathology.

There are also some other biomarkers that people sometimes use, including neurofilament light. And this is a marker of the axons of the nerve cells, the kind of connections between them. When they're damaged, they release this neurofilament light (NfL). And this is associated with many different disorders. So not just Alzheimer's but all kinds of issues. And so it's sometimes hard to know how to even use that one. And it also goes up with age.

And then there's another protein called glial fibrillary acidic protein GFAP that has some similarities to NfL in that it's very nonspecific, but it reflects some degree of inflammation. So those are the ones that are typically included in these profiles. But by far the most important one is p-tau 217. There are tests that combine these together. And that can be an additional approach that's useful in having a high accuracy test.

NANCY KEACH: I'm going to get to who should get that test and how you should ask

your doctor and stuff like that for a p-tau 217 test. I just want to ask two things really quickly. It's confusing that it's called p-tau 217. Is it measuring tau or is it measuring amyloid?

DR. SUZANNE SCHINDLER: So this is confusing. So tau—

NANCY KEACH: And I should say, sorry, these are two proteins that you find in the brain that are associated with Alzheimer's disease.

DR. SUZANNE SCHINDLER: So yes, it is confusing that this p-tau 217 is a better biomarker of amyloid than amyloid beta 42/40. That is very confusing. But what we find is that as these amyloid plaques deposit in the brain, the rest of the brain doesn't like it, and that changes. It responds. And something that happens is that there changes in this tau protein, and tau gets a phosphate group stuck on it at position 217. And then this tau is somehow released. And we can measure it in the blood. And it turns out these levels of p-tau 217 are much more strongly associated with the amyloid in the brain than the amyloid beta 42/40, which is not what you'd expect. But that's clearly what we see.

And it does appear that this p-tau 217 is some kind of injury response or some kind of response to amyloid pathology in the brain because the levels of p-tau 217 are more strongly associated with amyloid pathology than tau pathology. So it's very interesting how the brain works.

NANCY KEACH: And we don't, as patients and families, we don't really have to know that. But I always find people are trying so hard to understand this and know practically what they can do with these tests, what they do, what they don't do, how to get them. And it's just everything about it, in a way, is confusing. Paula asked, "Does this only check for Alzheimer's or for all kinds of dementia?" And I was going to ask that later. But I think it goes a lot to the question about what a biomarker is and how these blood biomarkers are used specifically for Alzheimer's.

DR. SUZANNE SCHINDLER: Sure, so it does depend on which biomarker. But the p-tau 217 base test, so p-tau 217 concentration or this p-tau 217 ratio, it's very strongly and specifically associated with amyloid in the brain, in particular in Alzheimer's, and is not well associated with other forms of dementia. There are some caveats to that, but just generally it really is a specific biomarker of Alzheimer's disease. That is not the case for neurofilament light or GFAP. But p-tau 217 is really quite good for specifically identifying Alzheimer's.

NANCY KEACH: So p-tau 217 blood test specifically for Alzheimer's. And I'll just quickly

ask you, so are there blood tests for other types of dementias, like Lewy body dementia, FTD? And you don't have to go into what they are because we've done separate programs on those specific types of dementia. But several people asked.

DR. SUZANNE SCHINDLER: Yes. So there's a lot of work on developing these tests. And there's been some promising candidates found. But in the clinic right now, there's really not clear tests for other neurodegenerative diseases, with the exception of neurofilament light, which is sometimes used to help diagnose frontotemporal dementia. But in most patients, neurofilament light does not add a lot of value. So in the future, hopefully we'll have a whole panel of tests that helps us to diagnose these neurodegenerative conditions. But right now, it's really Alzheimer's. So these blood tests are helpful in telling us, is it Alzheimer's or not.

NANCY KEACH: I'm going to stay with the p-tau 217 for a second, because there were so many questions about the ranges and what they mean. So Robin asked, "Can you please better explain the p-tau 217 levels." This is her, so I don't know if this is accurate. She says, "If anything above 18 is considered elevated tau, what number ranges are considered low, mid, and high levels of tau and what they mean?" And so this is why I know there's confusion between what's tau what's amyloid. But so people are hearing that they get a level and they don't know what that number means.

Gail from Newton, Massachusetts wrote, "What does it mean if your blood test comes back indeterminate?" Julie wrote, "My parents did not have Alzheimer's and dementia and lived to their mid to late 80s. My p-tau test showed 19. Should I be tested periodically to watch p-tau?" So can you give us an across the boards primer because there were probably 30 questions. We had over 200 questions for this program submitted in advance. What are the ranges? How do people know what, roughly, what they mean? And of course, then they talk to their doctor.

DR. SUZANNE SCHINDLER: Yeah, so very practically relevant questions here. The issue is that the numbers are all different for different tests. So if your number is 18 that doesn't tell me whether it's normal or abnormal. Because you have to know what exact tests. That test should come with a report that gives you a reference range. What a reference range is, it tells you that the range of values that are normal for that particular test. But there's not, in general, across the board, ranges just for p-tau 217. It all depends on the specific test and even the specific labs. So different labs have different reference ranges.

So I'm sorry I can't give you one number. But you'll have to go back to the test results or the test report that gives you that reference range. And just generally, though, we

know that these p-tau 217 levels have slowly increased over time. And right now, there's generally not a strong rationale for testing multiple times. And really clinically, they should just be used to test people who have cognitive impairment. With the question of is there cognitive impairment related to Alzheimer's disease pathology or not? And what we see is that these test results don't change very much, year to year. So doing it a year later is not likely to give you much of a different answer.

NANCY KEACH: It's actually wonderful to hear you say, it's complicated. It's complicated. There's no one answer. Because we all get really frustrated. And so do the doctors and other medical staff in primary care. It's very hard for them to follow all of this. And I know you do a lot in trying to teach them as the research is moving forward so quickly now. But tell me if this is correct. Right now, like a p-tau 217 blood test, I want to just talk about who should get it and what it tells us.

Because Barry Price wrote in something I was going to get to later, "What percentage of people who show a high marker show no behavior or signs of Alzheimer's?" So you could have a high p-tau 217 level and not develop Alzheimer's or any cognitive impairment. You could have a very reasonable or low level on your p-tau 217 marker and still develop some type of cognitive impairment. So these don't really predict your future. They are really, at this stage, telling if you have these particular types of proteins and how much and so they're going to tell you whether a certain type of treatment that attacks those proteins will work on you.

Because you don't want a treatment that's going to attack amyloid, let's say, if you don't have amyloid in your brain. And whether you're eligible for certain clinical trials. So I just wanted to put that out there to let you give us a more in-depth answer about practical use right now and appropriate use. I know you said let's please focus on appropriate use. Who should get these tests? Who should ask their doctor for this test? Who should not, and why? And what we will actually be able to ascertain from the blood tests today?

DR. SUZANNE SCHINDLER: These are really critical questions that lots of people are asking and thinking about. The first thing that I'll talk about is testing in cognitively unimpaired individuals. So there are consensus recommendations from the Alzheimer's Association and other groups thinking about this. And at least right now, I think most clinicians do not recommend doing these tests-- any kind of biomarker test blood, spinal fluid, PET-- in individuals who are cognitively unimpaired.

But in research studies and clinical trials, we do sometimes perform them in cognitively unimpaired individuals. And we do see that higher levels are associated with future

risk of cognitive impairment. So they have a lot of promise. But right now, the issue isn't so much the science, it's the practicality. There's not a specific treatment that we have available-- FDA approved-- for patients who are cognitively unimpaired who have elevated biomarkers right now. So there's not an additional medication I could prescribe people if they do have positive biomarkers.

Nancy, as you were talking about, there's lots of people who are biomarker positive who have these early plaque and plaques and tangles, who will never develop symptoms during their lifetime. And so that's just something to consider that it's not telling you for sure whether you're going to get it during your lifetime. And there's also potential risks. And these may vary depending on who you are. But imagine you do this testing when you're younger and it's positive.

Maybe you will lose your eligibility for certain forms of insurance, so that's possible. Maybe if you're still working and your boss finds out about it, they'll be like, oh, I don't know that I want to promote him to this next role because I'm not sure what's going to happen. There's a real risk of discrimination. And it also affects the way people think about themselves and their future. On the other hand-- just trying to be balanced here-- some people really want to know. And they say, this is my body, this is my life. This is my greatest fear, that I'm going to develop this. I should be able to find out. And I think that's important to consider, too, that some people really do think that this information would be helpful to them.

However, as a clinician, at this point in time, my recommendation for cognitively unimpaired individuals is not to do testing. Now, let's talk about people who have symptoms. And those are the people that I see in my clinic. And really, what these tests are designed for is-- in people who have symptoms, what is the cause of their symptoms? Is it Alzheimer's, diseased brain pathologies, these amyloid plaques and tau tangles? Or is it something else? And when the results are negative it's really, really helpful. And we look for other things and often find them.

When the results are positive, we still have to go looking for those things. And we still have to find all the different factors that are contributing to cognitive impairment. But in some cases, the primary cause is clearly Alzheimer's. And then for those patients, we might for example, think about referring them for amyloid targeting treatments. So these tests can be very impactful. And many patients really appreciate knowing their diagnosis.

And it does help with their future planning. And it also helps their family. Their family's like well, mom and dad were going to buy, another two story house. But now maybe

we should have them move closer to us in case they need more help. Very practical things. So I think that the context of use really depends on the patient and the risks and the benefits are very different for cognitively unimpaired and cognitively impaired individuals.

NANCY KEACH: Thank you for that. And I guess in the most practical sense, for Alzheimer's specifically, the test can give you an earlier diagnosis or potentially a more accurate diagnosis. And now that there are FDA approved treatments and probably more of those coming down the pike with 152 drugs in 198 clinical trials this year. The earlier you find out if you have these pathologies, the more chance you have of getting treatment. And so that's the basic-- but if you are pre-symptomatic, that is a little more complicated.

And I think why it's very confusing to all of us, is that there are clinical trials now starting on people who are pre-symptomatic and don't have symptoms but have amyloid or tau in their brain. And so it's very confusing to know those trials are happening or about to happen and happening. And yet, for diagnostic purposes, for most of us, as you say, unless you are really, I want to know this. I want to know it early. You're willing to suffer the risks, like an insurance carrier or an employer using this information in a way that you're not comfortable with. Early diagnosis, I just want to make sure we're hitting that, early diagnosis, how critical it is and how these blood tests are really helping that.

And Sara wrote in as you were talking. "Both my brother and I have been diagnosed with dementia, which we inherited from our mother. Should we have these tests?" So I'm asking this again just to clarify. They've been diagnosed with dementia, she says. She doesn't say which type specifically. So is that a case where somebody should ask their doctor for an Alzheimer's blood test?

DR. SUZANNE SCHINDLER: So that's an interesting question. So we do test typically to help patients-- to help them answer questions, to guide their management. If I have a patient, for example, who has severe dementia and I'm going to do the same thing regardless of the test result, then I'm not going to do the test. So really the question for her, I guess, would be how would the test results, finding out that the dementia is due to Alzheimer's disease, would that affect you in some way? Would that affect the way you thought about your disease? Would that affect your management? The treatments that are available to you. If the answer is yes, then yes. It makes sense to do that test, if you want to know that answer. But if you think you would do exactly the same thing regardless of the answer, then it may not be worth doing the test.

NANCY KEACH: Recently, there have been-- recently, I mean over the past year or 2-- FDA approvals of particular biomarker tests. So my first question is, if you do ask your doctor for a test and you want this test and you want to know a diagnosis, is it important that you say, I want a test that has been FDA approved? And can you say which are the FDA approved tests? Are you able to do that?

DR. SUZANNE SCHINDLER: Yes. So there's been four tests that have been cleared by the FDA over the last two years. The first was the Fujirebio p-tau 217/A-Beta42 test. The second test was the Roche Elecsys p-tau 181 test. The third test here recently was the C2N PrecivityAD2 test. And then the fourth test was the Roche Elecsys p-tau 217 test. So those are the four that are FDA approved. What I would also add is that we know that the p-tau 217-based tests are more accurate. So there's three of those. That's good.

And these are tests that basically any clinician can order. So it's not just me as a neurologist. Any nurse practitioner, medical doctor that's licensed can order these tests. And they are ordering them because patients are coming into my clinic having already had these performed. So there's multiple tests available there. And then there's additional tests that are-- we call them laboratory developed tests-- that have not yet been cleared by the FDA. Some of them are currently under review by the FDA. And they're still available.

In terms of, should we get FDA-cleared test or not. A lot of this comes down to practical issues. So oftentimes, doctors don't get a choice about what's available to them. Their health care system has a default choice in electronic health records. And they have to click on that. But it makes sense to me that if there's four tests that are FDA cleared and they've shown demonstrated higher performance, I would probably try to go for that, if that were possible. That said, I know that a couple of the laboratory developed tests that aren't cleared are pretty high performing. But yes, generally I would certainly recommend going with the FDA cleared tests.

NANCY KEACH: I got a bunch of questions-- and we always do when you come on, Dr. Schindler-- from doctors, that are clearly from doctors and scientists. And while I try to keep this really for patients, I'm going to kind of back in. Clifford from Baltimore wrote, "If a primary care physician finds mild cognitive impairment on testing, like from a MoCA or MMSE, a cognitive test, can that physician order these blood tests? And if the blood test is positive, can he or she initiate a brain MRI, a neuropsychological consultation for early lecanemab or donanemab?" Those are the drugs that are approved, the monoclonal antibody drugs, without the time-consuming brain amyloid tau PET scans."

Now, and I know we talked about this earlier, but I want to do it from the doctor's point of view because a lot of doctors watch this and you teach them. And Brian from Fishers, Indiana, who's also a physician, "Can you describe the patient profile that should or should not get a blood based p-tau 217 test?"

DR. SUZANNE SCHINDLER: Yes. So those are very common questions from physicians. So the answer to the first question, I talked some about this. But the basic answer is if you have a patient who has a typical AD dementia syndrome and you haven't found other potential causes that are likely causing the cognitive impairment, and they have a clearly positive blood test, at our center at WashU, we will take them through the pathway and start them on amyloid targeting treatments without additional tests. And that's because when you do the math, the likelihood of amyloid pathology is near 100%. And doing additional testing is not going to change anything really. And actually it just delays the process.

NANCY KEACH: And it's expensive.

DR. SUZANNE SCHINDLER: Yes. Here at WashU, we feel very comfortable starting appropriate patients, select patients on treatments without doing a PET scan or CSF test, based on the results of the blood test.

NANCY KEACH: Alana wrote, "How can or will blood testing for Alzheimer's be integrated into routine medical testing?" Will it? And she was talking about prenatal testing, routine wellness blood work. Shayna from Crofton, Maryland, "How early can you detect the markers? Should my young kids get tested?" I think you've kind of addressed this, but there are-- I just want to make sure we're clear. And then Woody from Knoxville, Tennessee, asked a really interesting question. "If AD has already begun, will the blood test identify stages or progression, like in cancer?" So can you use these blood tests show progression? Should your kids get this? Can you answer some of these practical questions?

DR. SUZANNE SCHINDLER: Yeah, these are a lot of different issues. I did want to go back to one other question that was asked about profiles of people appropriate for testing or not. One point that I did want to note is that these blood tests may not perform consistently in people with certain medical conditions. So the big one we worry about is chronic kidney disease. There is evidence that some of these ratio based tests may do better, may perform more consistently in patients with chronic kidney disease as compared to just a simple concentration. So that's something to consider.

When I have a patient who has more severe chronic kidney disease, I don't do a blood test. So I do a PET scan. So there are some factors like chronic kidney disease, other

more severe metabolic issues that make me not choose a blood test. And there's other factors that make me want to do CSF tests. So there are appropriate contexts of use and profiles that go along with each biomarker test. But I think that blood tests can be used in probably at least 80% of patients. It can be helpful in those patients.

And then, I'm sorry if I'm missing some of this, but one question was about staging. And at this point, there is a new biomarker called eMTBR-tau243 that helps with staging. And there's been some recent work on that. Also, p-tau 217 by itself is a pretty good biomarker of how much amyloid and potentially tau there is. It's not perfect, but it gives you some ideas. However, we're still not quite there in terms of staging the disease with blood by itself. I'm hopeful that we'll get better at that. What one issue is kind of that we don't have biomarkers of all these other pathologies yet. And often it's not just Alzheimer's that's contributing to symptoms. It's all these other pathologies. So of course, things get more and more complicated.

The way that we follow patients is really clinically. So that's what we care about. That's what they care about. How their symptoms are doing over time, what their function is. So that's, in the clinic, that's how we follow people.

NANCY KEACH: I'm going to move on, even though I want to ask you 100 more questions about that. In particular, the biomarker that you talked about is in development sort of or tests for it or in development that could indicate staging. Could you just say the name of that again, because this is the first time I've heard it.

DR. SUZANNE SCHINDLER: So it's called eMTBR-tau243 and it's a protein that is strongly associated with tau levels. So p-tau 217 is more strongly associated with amyloid levels. eMTBR-tau243 is more strongly associated with tau levels. And as you noted, this is currently in research and development. But it does look like it may be a promising way to stage Alzheimer's pathology.

NANCY KEACH: So when you come back next year, hopefully we can ask you about that. We heard it here first. Let's just switch for a second to insurance coverage. And I know that you're-- I assume you are not an expert in this area, but that a lot of people ask you. John from Medford, Oregon, wrote "Any news on insurance coverage for this testing? How about Medicare or VA coverage?" Belinda from Honolulu, Hawaii, "What is the cost of the test?" Donald from Coon Valley, Wisconsin, "So which method is the cheapest and most accurate predictor of AD?" So can you generalize about costs and insurance. I know it's different across the country, but in the world.

DR. SUZANNE SCHINDLER: Yeah, so this is a big issue. So to start, it's helpful to put this in context. All of these tests are new. Like this is all new in the last five years. And

oftentimes, regulations and reimbursement really trail what's new. And so they haven't caught up yet. And what we see in clinical practice is that often these tests are actually being paid for. Or at least our patients are not complaining about getting bills.

And I do hear that they are sometimes being paid for. However, it's not consistent. So sometimes they're being paid for. Sometimes they're not being paid for. It's not always clear to us, the people ordering it, whether it's going to get paid for or not. And it's often not clear how much they're going to cost. There are some companies that do have patient assistance programs, so that can be a helpful thing for patients that are they're more cost-sensitive.

However, I have to say that I have a fair number of patients where I say, well, these are your options. There's the spinal fluid test, there's the PET scan and the blood test. And the blood test could cost anywhere from \$200 to as high as \$1,500. And they're like, that's no problem. I'll pay for it. And because I don't want to do those other things. And so I do see that sometimes. And then other times people are-- give me the cheapest test. So I try to present options and then people make decisions based on that. At the end of the day, we very-- I don't know, just in our practice-- we've seen that they're often paid for, or at least the patients aren't upset about the bill.

Now, this is all silly, in my view, that these aren't paid for because PET scans are getting paid for most of the time. PET scans cost like 10 times more. So hopefully, things get straightened out relatively soon so that these tests, which are much less expensive, can get reimbursed. So we're not doing a \$6,000 PET scan when we could do exactly the same thing with a blood test that costs a couple hundred dollars.

NANCY KEACH: And I will mention that we're not going to get into policy today. As Partha wrote in, there is a bill in Congress called the ASAP Act. And for those of you who like to get involved in policy and advocacy, you should look at that. This will-- she writes-- this will allow Medicare to reimburse for blood tests for people without symptoms. Not passed yet. So you can look if you're interested at the ASAP Act.

I have a lot of questions about APOE4. And so I'm pivoting now to can you go and get a blood test for both for p-tau 217 and to find out if you're APOE4 positive? And I think most people at this point who attend this episodic series know what APOE4 is, but it's a genetic predisposition that increases your likelihood or your risk factors for getting Alzheimer's. So can you talk a little bit about APOE4 testing, and do you do it along with these other types of blood tests, or can you do it along with?

DR. SUZANNE SCHINDLER: So APOE, as you mentioned, is a risk factor for Alzheimer's and it's a gene. And so you have two copies, one from your mom, one from your dad.

The most common form is 3. So a lot of us are 3, 3, which is the neutral form. But if you have the E4 form, that increases your risk. If you have one copy, it goes up by about threefold. If you have two copies, it goes up by about 10-fold. However, it still doesn't mean that you're definitely going to get Alzheimer's disease, even if you have two copies or what we call an APOE homozygote.

So before these new amyloid targeting treatments were available, I actually had never ordered an APOE test. But now we order them all the time. It's part of the standard of care for working up patients who are interested in these treatments. Because people who are APOE homozygotes are at higher risk of adverse events. We're still treating some of them, but we want them to understand what their risk is so they can weigh the risks and benefits. And so we perform these tests.

The one kind of challenging aspect of this is if you find out that you're an APOE homozygote, that means that any of your children have at least one copy. So it has implications, not only for you, but also for your children. So it's sensitive in that way. But yes, we're increasingly doing that. APOE tests are available direct to consumer. I do not recommend doing them, necessarily. Because again, they do not tell you definitively whether you're going to get Alzheimer's disease or not. And they may affect your eligibility for long-term care insurance.

And with both the biomarker tests and with the APOE genotyping, once you know, you know and you can't unknow it. And sometimes people wish they'd never gotten the test. So I wouldn't recommend doing it. We do it clinically in this very narrow context of trying to understand people's risk for adverse events related to these amyloid targeting treatments. Again, that's very narrow context.

NANCY KEACH: You've approached this a few times. I'll ask it directly. Or Colleen from Knoxville, Tennessee, will ask it. "I'm curious about what happens when people receive false positive results?" There's also false negative results.

DR. SUZANNE SCHINDLER: Yes.

NANCY KEACH: Also, and it may be too early to know. We talked about this a little bit. What percentage of people who test positive for significant levels of amyloid and tau never develop cognitive impairment? So a percentage there. So sorry, two different questions there.

DR. SUZANNE SCHINDLER: In terms of false positives and false negatives. So this is one reason why accuracy is so important. We're doing these tests to help us understand whether this pathology is present or not. And that information is only useful

if we have high confidence in the results. So, very important that we use accurate tests. And it turns out that the patients that we're performing them on directly affect the likelihood of false positives and false negatives. So to illustrate that, I'm going to give you an extreme example. So this is not a real example.

But imagine that you have an 18-year-old who's cognitively unimpaired. And you do one of these tests and it's positive. What's the likelihood this is a false positive? So it's extremely high. But imagine instead you do the test on someone that's say, 90 years old who's had Alzheimer's disease, dementia for five years and you get a negative result. So that's actually a fair likelihood that that's a false negative. So this is why clinicians still need to be involved in all of this. Because there are false positives and false negatives.

And the examples that I gave you were extreme. But in clinical practice, we see much less extreme examples. So we see the 60-year-old with fluctuating cognitive impairment who has a kind of borderline positive result. And since I'm a clinician, I've done a lot of testing. I know that I'm worried that could be a false positive. And I do another test. But folks who just get that result might think it's definitively positive. So that's why it's important to continue to have a clinician involved with interpreting these results and thinking about next steps, because we do have to consider the clinical context.

And then the other question was about what rates of people are cognitively impaired and have positive results. So it's strongly associated with age. So the older you are, the more likely you are to have a positive test, even if you're cognitively unimpaired. And so when you get to be in your 80s, the likelihood of having some of this amyloid and tau pathology in your brain is really high, even if you're cognitively unimpaired. So we're getting to 30,40% or higher, depending on the age group. And again, that doesn't necessarily mean you're going to develop dementia. But you're certainly higher risk. But that's again one reason why clinicians still need to be involved with understanding what these results mean.

NANCY KEACH: Thank you. Yeah, and the question was actually about on the percentage of folks who may be positive but will not develop. But I know these are very hard figures to come by.

DR. SUZANNE SCHINDLER: Yeah and so I do think that that's hard because it actually depends on the rate of death, mortality. Because people are more likely to pass away from other causes. So it all depends on the age group. And so if you're 90 years old and you live to be 95, and you're 90 and you just became positive and started to develop these symptoms, then you may never develop symptoms during your lifetime.

Now, if you're 60 and become positive that-- you have longer on average to develop symptoms. So there's not one percentage. It has to be highly age stratified and also stratified for health conditions. So it's a complex it would be a very complex answer.

NANCY KEACH: There's two final questions that I wanted to go. And one has to do with privacy, which you touched upon. Are there any protections if people-- I'm a want to know person, OK. I got tested 10 years ago to find out my APOE4 status because obviously, I'm involved in all of this. And while I haven't had one of these blood tests, I would. If I had a concern, I would try. Because I know as a professional in this field, that would give me options for earlier treatment, for preparation, for lifestyle interventions, for all kinds of things. But is there anything in place to help protect your privacy if you do want to know, so that this information isn't going to be used against you in some way.

DR. SUZANNE SCHINDLER: So certainly there's HIPAA, right. So you to some extent don't have to disclose this. So for example if you get tested, I wouldn't recommend telling your boss the results. Or other people where you lose control over your own personal information. So I would try to keep it private because again, once people know they can't unknow it. But in terms of legal protections, it's pretty limited. And it's also in your medical record. And that can influence whether you have access to a long-term care insurance or other kind of benefits. So the protections are limited. Actually, part of the ASAP Act that was mentioned is about those protections. So I think those protections are really important. But they right now really don't exist. Obviously, for some people it doesn't really matter or not if people know. People are open. Other people, it could have major impacts.

NANCY KEACH: Yeah, absolutely. And I've seen many people who are diagnosed who are still running companies and things like that. It's very complicated and it's very individual.

And I'm going to start to wrap up now, but I want to thank you especially for coming on because as we can tell in this hour, all of this research is new, thanks to a lot of funding that's been going towards Alzheimer's disease that unfortunately, there have been a lot of funding cuts for scientific research. And this is why scientific research is so important. This is why clinical trial participation is so important. Because the field right now is moving forward so rapidly. But folks like Dr. Schindler have to be brave to come on, because a lot of times the questions, as we've seen, are kind of, I don't know or we don't know this yet or this is in development. So thank you, as always, for coming on.

So as our time today comes to a close I have something to announce to everybody,

in particular if you or someone you know is living with Lewy body disease. There is a documentary filmmaker, his name is Tylor, who did Robin's Wish after Robin Williams passed away with Lewy body dementia. And he did a follow on documentary called Spark, which talked a little bit more about the science of Lewy body dementia. He is doing another documentary now that will be called Spark II. And even though it's a documentary, they're doing what they call a casting call. They want people who are living with or caring for people with Lewy body dementia to participate in this film. So if you or someone you know would be interested in participating in this film, please email tylor@quotablepictures.com.

So I'm going to just try to thank my colleagues at BrightFocus Foundation, Dr. Sharon Rossi, producers Amanda Russell and Alexa Villarreal. The team at M Squared, who provide this platform for us. And especially, thank you, Dr. Schindler, so much for sharing this information in progress with us today. Really appreciate your time.

If your questions were not answered today, if you had questions on other topics, which I'm sure you do, there are 47 prior episodes of this program that are free and available online at BrightFocus.org/ZoomIn. Or they're on BrightFocus Foundation's YouTube channel or our Alzheimer's Disease Research Program channel. The scientists that are giving their time for this program are just fabulous. They are the top of the top. So please do access those other programs. If you think this program would be helpful to somebody else you know who's going through this, please share this link with at least three friends. BrightFocus.org/ZoomIn.

We've just been very lucky to have agreement from Dr. Paul Newhouse, who's at Vanderbilt, to come on our Clinical Trials series. As I think some of you know, every other month, we focus just on a clinical trial or a group of clinical trials that are actively recruiting now. And so on October 15th, Dr. Newhouse is going to talk to us about the MINDSET trials and any other trials that are active and recruiting related to KarXT or KarX-EC.

And I'm going to close, as I always do again by thanking you all so much for participating and being with us. We're really grateful that you're here with us for this journey. You're not alone. We are here for you, and you are all here for each other. There's so many people going through this. And as I always say, life is so short. Tell everyone you love how much you love them. Give them a hug. Keep them close to you. I hope you have a great day. Until next time. And again, thank you, Dr. Schindler, for participating.

DR. SUZANNE SCHINDLER: Thanks so much, Nancy, and thanks to everyone for

participating.

NANCY KEACH: We'll have you back soon, I hope, to talk about new developments.

DR. SUZANNE SCHINDLER: Hopefully we'll have lots of advances to report.

NANCY KEACH: I'm sure we will. I can't wait for CTAD, which is the scientific conference that happens every November. There will be a lot of new announcements, we hope, in October and November on clinical trial results. Somebody actually asked about AHEAD 3-45 in here. And I know that just several trials will be reading out towards the end of the year. So stay with us and keep registering. And tell people about our program and also our Let's Talk Alzheimer's podcast. And again, everybody have a great day.

Resources:

- FDA Approved Blood Tests
 - [Lumipulse G p-tau 217/β-Amyloid 1-42 Plasma Ratio \(Fujirebio Diagnostics\)](#)
 - Elecsys p-tau 181 Plasma Test (Roche Diagnostics)
 - PrecivityAD2 (C2N Diagnostics)
 - Elecsys p-tau217 Test (Roche Diagnostics (in collaboration with Eli Lilly and Company))
- [FDA Clears Two Alzheimer's Blood Tests](#)
- [ASAP Act](#)