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

How Is Dementia Diagnosed?

Thursday, October 17, 2024 | 1 p.m. EDT
Transcript of Zoom with David M. Holtzman, MD
Barbara Burton and Reuben M. Morriss III Distinguished Professor
Director, Knight Alzheimer's Disease Research Center
Scientific Director, Hope Center for Neurological Disorders
Washington University School of Medicine, Department of Neurology

The information provided in this transcription is a public service of BrightFocus Foundation and is not intended to constitute medical advice. Please consult your physician for personalized medical, dietary, and/or exercise advice. Any medications or supplements should be taken only under medical supervision. BrightFocus Foundation does not endorse any medical products or therapies.

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

NANCY LYNN: Thank you all for coming, those of you that are on Zoom and those of you that are on YouTube. I'm Nancy Lynn, Senior Vice President for BrightFocus Foundation. BrightFocus Foundation has funded over $300 million of research globally to understand and treat and cure Alzheimer's disease, macular degeneration, and glaucoma.

And we are really delighted today to have Dr. Dave Holtzman talking with us about how dementia is diagnosed. I want to mention that this program is supported in part by educational funding from Biogen, Lilly, and Genentech. And we're very grateful to them for letting us bring you this informational programming.

I'm going to introduce Dr. Holtzman. And we'll jump right into the topic since it's a big topic. So David Holtzman is professor, scientific director of the Hope Center for Neurological Disorders, principal investigator of the Knight Alzheimer's Disease Research Center, and former chair of neurology at Washington University from 2003 to 2021. Some of his lab's accomplishments include showing in part how APOE contributes to Alzheimer's disease, development of plasma and cerebrospinal fluid biomarkers for Alzheimer's, and demonstration that synaptic activity and sleep affect amyloid, beta, and tau levels. These are proteins in vivo. Several of his honors include being a recipient of the Potamkin Prize and MetLife award for research on Alzheimer's, Rainwater Prize for outstanding innovation in neurodegenerative disease research, election to the National Academy of Medicine, and being appointed to the National Advisory Council of the NINDS and the National Institute on Aging. Dr. Holtzman has trained over 70 graduate students, postdoctoral fellows, many of whom have gone on to successful careers in academia and industry. And BrightFocus has been incredibly proud to be a funder since he was a young pup and a funder of some of his graduate students. So welcome.

And finally, the next slide, a lot of people write in questions on subjects that don't relate to today's episode, which is how to get a diagnosis. So if your questions are other, like, what is Leqembi? Or what is Kisunla? Or how did genetics affect my chances of getting Alzheimer's disease? There are episodes on all of those subjects. So these are all free and online at our website, brightfocus.org/zoomin. And they're available on YouTube. So we're trying to get that to you. And please don't hesitate to go watch those episodes. There's great information in them. So let's put up the next slide. And I'll introduce Dr. Holtzman. Thanks so much for being here today.

DR. DAVID HOLTZMAN: Thanks for the invitation.

NANCY LYNN KEACH: So I put this up really just to give us a framework to kick off. And we can always refer back to this, getting a diagnosis. It's really problematic and difficult area for a lot of people, is how do you get a diagnosis for dementia, for Alzheimer's. So before we jump in-- and let's take down the slide for now Dr. Holtzman, why is it important to get a diagnosis as early as humanly possible? Because a lot of questions are about when to try to get a diagnosis.

DR. DAVID HOLTZMAN: Well, I think it's just for any kind of medical condition, whether it's outside the brain or inside the brain, it's super important to get an early diagnosis because they're often able to do different things that are about that disease. Let's say in this case dementia, if you're diagnosed very early, there's different treatments that can be made available that are more effective if you start early. You also want to make sure that whatever might be causing this-- there's a lot of things that can cause dementia. And so some of those are immediately treatable. Some of those are not. But I think you need to understand what's causing the problem with the brain as soon as you can to have the best chance of doing as well as you can for as long as you can.

NANCY LYNN KEACH: Yeah, and we know that researchers are moving to try to detect the disease earlier and earlier with the idea that if you can actually detect it before symptoms begin, you have a better chance of slowing it down or preventing it. So they want to go as early as possible. So where do people start? Where do people start if they want to get a diagnosis?

DR. DAVID HOLTZMAN: Well, I think once something is detected by either the person themself-- or in the case of dementia, often by loved ones, whether it's a spouse or a friend, relative-- that it's really important to see get seen by somebody who knows how to best diagnose this and the right ways to go about it. So a lot of people, it often might be talking to their internist. But at that point, usually, because just like in any specialty area of medicine, the experts on this are typically that you would get referred to for a more definitive diagnosis might be, in the United States, it's usually a neurologist with specialty area in this topic. But there's also a number of geriatricians who also specialize in this as well as some psychiatrists. But for the most part, it's a neurologist with specialty area related to this topic.

NANCY LYNN KEACH: Can a general physician give a diagnosis? Or can only a specialist give a diagnosis?

DR. DAVID HOLTZMAN: No, a general physician can give the diagnosis. It just really depends on their expertise at how much to trust that or not. It's not that a general physician can't. But just a general physician needs to know about so many different diseases and their expertise about this topic. It may be really good. But it may not. It really depends on their background and what they're staying up with and things like that.

NANCY LYNN KEACH: So when people go to the doctor because they're concerned and the doctor says, oh, it's nothing, come back in a year, and then they do the same thing the next year, that may mean that the doctor doesn't have as much knowledge as they might. It may mean-- and I have Paula from Elk River, Minnesota, who writes, when neurologists give no working prognosis or diagnosis after two or three years, is that malpractice? Are they just milking us for the fees?

DR. DAVID HOLTZMAN: Yeah, I'm not 100% sure what-- I assume the question has to do with if somebody is seen by, let's say, a neurologist and the neurologist thinks that something is wrong and they don't then say what they think is the cause or they can't at least give some idea of what might happen, that's not the person you want to continue seeing because you at least want to get an answer to those questions. It may not be that we know 100% as the evaluating physician how the person is going to do. But at least we should be able now to give the best diagnosis we possibly can, at least guesstimate what's going to happen, based on our experience in the literature, et cetera.

NANCY LYNN KEACH: And so back how to get a diagnosis, you started with reporting from your own concerns or your family's observations. So it's important for them to give their physician, whether it's a primary care or geriatrician or a neurologist, a review of symptoms. So the first thing you were also referring to is ruling out other conditions because you said what there are different things that cause dementias. So can you just elaborate on that a little bit?

DR. DAVID HOLTZMAN: Yeah, let me step back because I think one of the most important things in the diagnosis-- and I did mention this before, but I want to highlight is that it's critical for the physician to get the history of what's going on from a person other than the patient in addition to talking to the patient. This isn't typically done in most other medical conditions. Usually, most of the information is gathered from the patient themself. But when there might be trouble with memory or thinking, it's critical to talk to people that have observed the person over time so you have potentially more reliable information about what's been happening. That's one thing.

But then in terms of-- if the physician and the family-- and they do think something's been changing-- the cognitive memory, other language, other areas of thinking are declining-- there's lots of different diseases that can cause decline in memory and thinking. One of them is Alzheimer's disease. And that's common, especially as we get over 60, 65 years of age. That is the most common disease that causes dementia.

But there are many other diseases that can cause dementia. Some of them, you want to know about immediately because you would do something about that. So for example, sometimes people have blood bleeding into the brain or around the outside of the brain called a subdural hematoma. And even though you'd think the person might present with a focal neurological deficit, like a stroke, that's not always the case. Some people present with just a slow decline over a few weeks or months with memory and thinking. And that would be treated by draining the blood out of the brain. So that's an example why you-- you always want to-- if somebody is developing decline in memory and thinking after you take the history and examine the person, you want to obtain an imaging of the brain to make sure that there's not bleeding, a brain tumor. But also, you can get an assessment of the structure of the brain. And if it is due to a disease that is a degenerative disease, like Alzheimer's, or other disease, like frontotemporal dementia or Lewy body disease, the pattern of the brain structure can look different in these different diseases.

NANCY LYNN KEACH: I'm glad you mentioned that because I'm going to ask a little more about that later. And Jay, who put some questions about blood tests and PrecivityAD2 to in the chat, we're going to get to that as well. Just want to start with some of the basics first.

So we talked about ruling out other conditions and getting a family history. So let's talk about what we would call, say, the most standard cognitive tests. Or I used to call it pencil and paper. But it's not pencil and paper anymore. Can you talk about the few most commonly administered cognitive tests?

DR. DAVID HOLTZMAN: Yeah, the most common in most practices where people are evaluating people for dementia-- the relatively short tests are things like the Mini Mental State Exam test or the MoCA or Montreal Cognitive Assessment or the Short Blessed Test. These are basically a series of questions that assess things like short-term memory, orientation, simple problem solving, and language. But they don't go deep into any of those areas. But they give a general feeling for whether some of those areas are normal or not normal.

NANCY LYNN KEACH: So those are short. And those are usually at the beginning.

DR. DAVID HOLTZMAN: Yeah, each one takes a few minutes to do. If you do, let's say, for example, the Mini Mental State Exam and the Short Blessed Test, that might take six minutes to do both of them.

NANCY LYNN KEACH: And I will mention that there are a lot of other types of assessment tools, including even one Brain Guide, where you can call on a phone and it's a very preliminary type of assessment. But for people who are not near a physician or an academic medical center, it's at least a way to start. So if anybody has a particular interest in trying-- you can't reach a doctor's office, you can email us. And I'll let you know of a few tests that you may be able to take just to give you a beginning indication of whether or not you ought to make that trip to try to find a professional. And, Dr. Holtzman, Kathy from Newtown, Pennsylvania, "Is a neuropsych evaluation always included with those other tests?" A lot of people ask about neuropsych.

DR. DAVID HOLTZMAN: So in clinics where the physicians are expert in dementia for evaluation, I would think that most of those, if not all of them, do some sort of neuropsychological testing. That can either be done by a tester that's affiliated with that physician, where they just administer the tests. In some cases, there are neuropsychologists where a person would see them separately than the physician, where they administer a much longer series of neuropsychological tests that can take an hour or two hours to administer. But every practice is a little bit indifferent as to whether you go to separately to a neuropsychologist or just get a battery of neuropsychological tests. When you see, let's say, the neurologist, for example. But yes, they generally are done. They're more extensive than just those short tests.

NANCY LYNN KEACH: So it's not really as if you could say you can only get a diagnosis if you get this and this and this and this and this. But a neuropsychological test will usually be included to get a more accurate diagnosis.

DR. DAVID HOLTZMAN: Actually, in my view, most of the neuropsychological tests are helpful to quantify the current state of the person. They don't give you the diagnosis. But they stage where you are at that time. I actually think the history from the informants-- friends, family, others-- is more useful to making the diagnosis than the neuropsychological tests. The neuropsychological tests are helpful to, again, see where one is at that point and get some little more feeling of what parts of the brain aren't working as well. So they're an adjunct to the diagnosis.

NANCY LYNN KEACH: So we had a lot of questions about when, like Jacqueline from Brooklyn, "My mother, who died at 95, had Alzheimer's for the last 8 to 10 years of her life. I'm 69. And I want to know if I have any signs of the disease. Can I get a blood test or a PET scan to find out?"

I have another one. "My father is currently in end stage. This is Janice from Plano, Texas. I'm 54. I would love to do everything possible to prevent this from happening to me. Where should I start? Where and when should I start to get evaluated?" So can you speak to that?

DR. DAVID HOLTZMAN: So I will have to just give you my own opinion about this. Everybody's opinion will be different and even other neurologists that do what I do. But I think right now, for clinical reasons, not research reasons but for somebody who's a patient who think they might have either increased risk or they might be developing the disease clinically, meaning symptoms and signs, the most important thing is really to get evaluated by a specialist to see whether or not they think they do have cognitive decline or not.

If they do, then a series of evaluations should be done to best identify what's causing that cognitive decline. We can get into the test. But I think for people that have no symptoms or let's say it's determined that somebody has no symptoms but they might have higher risk because of their parental history or their family history, I actually think the most important thing at this point would be if you really want to find out more information that is test wise to probably get involved in research studies at one of the many Alzheimer's disease research centers around the United States because a lot of the definitive diagnostic testing that can be done is currently only indicated for people that are symptomatic.

I think that's going to change in the future because using different tests, whether it's certain imaging tests of the brain for things like amyloid buildup or tau buildup or even some of the spinal fluid and blood tests, we know that we can diagnose the pathology, what's underlying Alzheimer's disease in the brain, many years before symptoms begin. But right now, there is no definitive treatment to give a person if that was found. There's nothing that we can really do from a medication standpoint. What you can do, of course, is optimize your ability to try to delay the onset of any kind of neurological disease by following things that I think are pretty now out there, like having an appropriate diet, not being overweight, making sure diabetes is treated or try to prevent cardiovascular disease, try to make sure that your sleep is optimized and your exercise is optimized.

But I'm not sure if you-- some people might want to know that they're at high risk because they might change their lifestyle in one way or another if they only knew their high risk. But in my view, you should probably be carrying out these important lifestyle things regardless of whether you're high risk because they're good for both your brain and things like Alzheimer's as well as for other parts of your health, like your heart and other things. But some people personally want to know-- I think most of the tests that are available, we cannot, as a physician, order them, at least to that are covered by insurance, if you're normal.

NANCY LYNN KEACH: Right. And that's the catch. It's trying to get a lot of these tests covered. And we're going to talk about that. So we talked about an entry level cognitive exam and neuropsych testing. And then we come to the lab tests. So can you just lay out what types of lab tests would be done and then what types of imaging tests?

DR. DAVID HOLTZMAN: Well, if the physician thinks that the patient is developing very mild changes in memory and thinking or whatever change and they think it might be due to Alzheimer's disease, because there are now treatments that one could consider that slow down the disease, like some of the anti-amyloid antibodies, we now are going forward in getting-- in addition to a brain scan, like a CAT scan or an MRI scan, to rule out other diseases, we're also obtaining tests to determine whether the person has amyloid deposition in the brain. So that's one of the proteins that's a marker for Alzheimer's disease.

So we now have three options. We can either order what's called amyloid imaging, where you can directly detect what's called a PET scan, whether amyloid is in the brain. It's a very accurate test. It's very expensive. But it is covered by insurance if you're being considered for treatment with one of the anti-amyloid antibodies.

So there's also spinal fluid testing, where drawing blood out of your arm-- a needle's put in the spinal fluid. And it's actually not dangerous. And it's actually not more painful than drawing blood if the person knows what they're doing. And that also can detect proteins in the spinal fluid that can determine if you have amyloid in the brain. And it's very accurate test. And those are both covered by insurance.

You can also now-- there are some blood tests. Not all of them. But some of them have been shown to be highly accurate, as accurate as the spinal fluid testing, for determining whether there's amyloid in the brain. Those can be ordered. Some of them are what are called CLIA approved tests, meaning that you can order them and they've been somewhat validated. But none of the blood tests, no matter how good they actually might be based on the literature, are yet covered by insurance. I expect that will happen in the near future but not at this point. So you can obtain them. But often then the person would have to pay for them out of pocket.

NANCY LYNN KEACH: There's a lot of confusion about this and a lot of questions about this. And we had talked about blood tests and blood biomarkers in a prior episode. And someone wrote in. She went to LabCorp. She got the test. It was something around $700 for her. She tried to get reimbursed and was told she could not get reimbursed. Her doctor had to write that it was a medical necessity to get the test. She tried to get the results. She couldn't get the results herself and couldn't read them anyway.

So we all realized that the scientific community is tremendously excited. And I know they've just concluded what they call a head to head test of different companies and different types of blood testing to see which has the highest accuracy. What kind of a recommendation can you make as to how we can bring the public, like the people on this Zoom and the doctor community and the insurers eventually, more up to speed so that they are understanding more of what you guys, the scientific community, are pioneering? How do we bridge this gap?

DR. DAVID HOLTZMAN: So I'll tell you what I do when I see patient who is developing cognitive impairment. After I do all of the things that we talked about earlier, I'll then talk to the person about whether to test for amyloid deposition in the brain, with the idea being that they might be eligible for one of the new treatments. And then I tell them, these are the things that can be done. We can either order an amyloid PET scan. And I mentioned it involves coming into a hospital, usually getting a small dose of radioactivity injected into your arm. It's generally very safe. And it's covered by insurance if you're getting it to evaluate for one of the new treatments. I say another possibility is we could obtain cerebrospinal fluid testing. And I go through what that involves. And then I will say there are blood tests that I personally think are as accurate as those other tests. And I'll mention that's an option for you to obtain. We could order that. But I do mention then it's not covered by insurance. So then I go through what the costs would be if we do order it. And then they let them make the decision if they want to go that route instead.

NANCY LYNN KEACH: Yeah, I had meant to read, Jay from Wooster, Ohio, "Can my primary care physician order a blood test from C2N diagnostics, PrecivityAD2, for example, to verify Alzheimer's?"

DR. DAVID HOLTZMAN: In that specific question, yes, you can do that as long as the physician orders it. And there are certain things, at least from that company, where they require a physician to order it. And they also tell in the recommendations that it's the indication to order it is somebody who has started to develop cognitive impairment.

NANCY LYNN KEACH: OK.

DR. DAVID HOLTZMAN: Now, that doesn't mean sometimes a physician will order it without necessarily following that. But that's what the company's recommendation is.

NANCY LYNN KEACH: And what can you see from these blood tests? I mean, you're one of the pioneers in this field. What are you looking for? And what do you think you'll be looking for in the future?

DR. DAVID HOLTZMAN: So what's done now-- well, the most accurate tests that are available measure a protein in the blood that is actually a form of the tau protein. It's called phosphorylated tau 217. Basically, it detects another protein, not amyloid-- another protein that gets released into the blood from the brain. And it starts going up. It's elevated when people develop amyloid deposition in the brain. So when the test is an accurate one, it's a very good indicator of whether or not someone has amyloid in the brain or not. And amyloid is one of the things that's required to have a more definitive diagnosis of Alzheimer's disease.

NANCY LYNN KEACH: And the field is extremely excited, and rightly so, about the development of these tests because they are quicker, cheaper, and ultimately as accurate, it seems, as some of the more expensive and more invasive tests. So how quickly do you see this becoming more mainstream or more commercially available and reimbursed?

DR. DAVID HOLTZMAN: My best guess is that probably by about a year from now, I would expect that some of these will be both not just available but covered by Medicare and probably FDA approved as well within probably by about a year, is my best guess.

NANCY LYNN KEACH: And I know you'll have to answer this from a personal opinion standpoint as well. So when we have someone like the lovely woman who was writing to us, what do you say to people who wonder, should I just go to LabCorp or Quest and ask for one of these blood tests?

DR. DAVID HOLTZMAN: In my own personal recommendation is to not do that because some of the tests where you can just go and not have this done through a physician are not necessarily the most accurate tests. And so if you get a result and it says-- for example, it suggests that you have amyloid in the brain, but it's not a very accurate test, then that's not going to help either the patient in terms of what you're going to do about it. So I think that's one of the reasons I really think it does need to go through physicians.

Now, there are certain tests that are available where a person can just get the test without a physician referring them. Those certainly are not covered by insurance, to my knowledge, if you're not referred by a physician. And also, the accuracy of the ones that are available that way, in my view, are not very good at this point.

NANCY LYNN KEACH: And I'm going to read a question from Anne on YouTube. And then I want to make a shout out, or I'll let you make a shout out to why it's always very helpful to participate in clinical trials to get good care. Anne from YouTube writes, "Can I use the Precivity test to monitor my amyloid and tau levels ongoing? I did the test a year ago. And I was positive for tau. I have done cognitive tests in a trial and have no cognitive symptoms yet."

DR. DAVID HOLTZMAN: The scientific answer is that it may be useful to get that in the future, given some of the research that's being done that suggests-- for example, in some of the phase III clinical trials for anti-amyloid antibodies done by Eisai on Leqembi and also with the Eli Lilly's donanemab phase III trials, those measurements, like the one that was described, they do respond to the therapy. But we don't know whether it's-- there's no recommendation yet as to whether to use that as a response or not. There's not a consensus in the field yet. And it's certainly not reimbursed to do that. But if you wanted to obtain-- if the physician wanted to obtain it, that individual physician might find it useful to give that information to the patient. But again, it would be something they'd have to probably pay for themselves. It's not going to be covered by insurance.

NANCY LYNN KEACH: And I think it's interesting question because-- so I'm going to use it as a generalized question. So if you've had the blood test and you're positive for tau but your cognitive tests are not in the questionable range, let's say, then what do you do?

DR. DAVID HOLTZMAN: Well, so again, one of the main reasons to get those tests would be because you are considering getting therapy, getting these new treatments.

NANCY LYNN KEACH: So I'm going to interrupt for one second to say we have full hour-long episodes on each of those two FDA approved monoclonal antibodies, Kisunla and Leqembi. So you can go on the website if you want to hear a full hour on each of those. And then we have some other episodes about new treatments too. So sorry, Dr. Holtzman.

DR. DAVID HOLTZMAN: So yeah, I think-- so the other thing is that when person comes in to be evaluated in there-- and let's say the physician with the family and the patient think, well, there may be some questionable impairment. The test like that might be useful to confirm in the physician's and the family's mind whether or not they think the questionable impairment is due to Alzheimer's disease versus something else. That might be a reason to get the test.

Another one would be if there is some very subtle impairment and it might be due to the earliest clinical phase of Alzheimer's, it's good to confirm that that's what it's due to. Again, because with these new therapies, if they're going to be as effective as they can be, it's best to start as early as possible. That's what the data from the clinical trials show.

NANCY LYNN KEACH: Yeah, early is our refrain. And I know this is a big subject. But I'm going to ask because there are so many questions related to genetics and in particular APOE4. But Kathleen Howland, who's here, I guess-- I don't know if you want to ask this yourself. But I will ask it for you. "Is testing for APOE4 useful?"

DR. DAVID HOLTZMAN: Well, so one, the APOE gene comes in three common flavors-- APOE2, APOE3 or APOE4. APOE4 as many of you are probably on have heard, it's the strongest common genetic risk factor for Alzheimer's disease. The risk varies based on your ancestry, actually. So if you're of European Caucasian descent, it's actually a very strong risk factor. Actually, of people of African descent, it's a risk factor but not as strong. But in any case, it's a very strong risk factor, the APOE4 form of the gene. Some people want to obtain that result-- know what their

APOE genotype or form is even if they're normal. And I personally don't recommend getting that if you're normal. But some people are curious. And it can be obtained in different ways by companies like 23andMe. You can get tested and other things. But it does tell you whether you're at higher risk or lower risk depending on your APOE form. But it's not a definitive-- it doesn't mean that you're going-- if you're APOE4/4, which is the strongest risk, it still doesn't mean 100% you're going to get Alzheimer's disease. And that's why these other tests, is there amyloid in the brain-- the test we just described are much better at determining whether the disease is starting in the brain or not than the genetic measurement.

NANCY LYNN KEACH: And there are as well some episodes on genetics and Alzheimer's, if you want to refer to those.

DR. DAVID HOLTZMAN: And we do obtain APOE testing in people that we're considering putting on the new therapies. And that's because the risk of the therapy is higher or lower depending on what APOE form you are.

NANCY LYNN KEACH: Right, the risk of the side effect risk profile is different.

DR. DAVID HOLTZMAN: Right.

NANCY LYNN KEACH: Melissa from Aldie, Virginia, wrote, "Just because you have amyloid in your brain doesn't mean you have dementia. So when will a doctor actually say a loved one has dementia?" And why is it that-some people will have a lot of amyloid, and they don't have dementia?

DR. DAVID HOLTZMAN: Well, so two things. One, there's a lot of different diseases that cause dementia, which is a decline in memory and thinking that impairs your function. Alzheimer's disease is one cause, as I said early on in the discussion. But it's not the only one. And some of the other causes don't have amyloid in the brain. There are other diseases. But really, the diagnosis of dementia is a clinical diagnosis. In other words, if somebody has a decline in memory and thinking that's impairing their day to day life, that is dementia. If it happens over a six-month period and it's continuing to progress, that is what the diagnosis of dementia means. It doesn't tell you the cause of the dementia, just that's how you diagnose dementia as a clinical diagnosis. But then the actual cause of that syndrome then needs to be determined as best you can because that's where the recommendations for treatment and also telling what educating the family and the patient about other things that they can do that could be helpful for them.

NANCY LYNN KEACH: Yeah, the most commonly asked question still, is, what is the difference between dementia and Alzheimer's? And I like to say it's sort of like you can say, I have a headache. But that doesn't tell you what the cause of the headache is.

DR. DAVID HOLTZMAN: Right, right.

NANCY LYNN KEACH: And so dementia is the condition. And Alzheimer's is one of the causes. And that actually leads me how to diagnose and distinguish different types of dementias. And Joanne from Missouri wrote, "How common is dementia due to two or more brain disorders, like Alzheimer's, vascular dementia, Lewy body dementia? And how do the diagnostics differ with multiple diseases?"

DR. DAVID HOLTZMAN: That's a great question. So when people develop dementia, if it's before the age of 70 when the symptoms start, that's often due to a single disease. But the older you develop dementia, which it becomes more common, of course, with age, the more likely that the contributor to the dementia is more than one thing.

The most common things are a combination of Alzheimer's disease pathology in the brain combined with cerebrovascular disease, like strokes, basically. That's the most common multi disease. But there's also other diseases that combine often with Alzheimer's disease, such as what's called Lewy body disease. And sometimes, there's these other-- I won't get into the minor details. But there's some other pathologies that also can contribute.

So in terms of trying to figure out if more than one disease is causing dementia, that's where not only the testing for this amyloid and tau proteins can be helpful for the Alzheimer part, but the MRI can be really useful to determine how much cerebrovascular disease-- how much damage from small vessel strokes, for example, there is. Or with Lewy body dementia, on top of Alzheimer's disease, there's often additional clinical features that are present that would indicate that disease, like some what we call Parkinsonism, where people get more stiff and slower with or without a tremor. If that's present on top of a history that also sounds like memory decline and trouble with problem solving, then that might be somebody who's developing Alzheimer's disease and Lewy body disease.

Unfortunately, we don't have great ancillary testing to be as definitive about the other diseases. But that's changing. So for example, there's a new test that can identify whether this Lewy body pathology is present. It's also not covered yet. But it's a spinal fluid test that can determine that you have this protein called synuclein building up in the brain that is indicative of Parkinson's and Lewy body dementia. So with the other relatively more common dementias, like frontotemporal dementia, we don't have a way to out what specific disease is causing that particular constellation of problems yet. But I think it will be there in the next years, I suspect.

NANCY LYNN KEACH: Yeah, it's so fascinating. Robin Williams had Lewy body dementia. But it wasn't diagnosed until after his death. And I know his widow for many years went around advocating for some way to diagnose-- for neurologists to recognize those specific indicators and symptoms. And same now with Bruce Willis having frontotemporal dementia. It's bringing a lot more awareness and, I think, actually driving the science forward to some degree. And Laura from Missoula asks, "Are there types of dementias that are impossible to diagnose definitively?"

DR. DAVID HOLTZMAN: Yeah, for sure. There are some of the more common late life dementias but we don't have good tests for. There's one that has a new name the acronym is called LATE. But bottom line is that some people develop a particular pathology with a protein called TDP-43. Anyway, it builds up in some older people, specifically in the memory part of the brain, the hippocampus. So sometimes, people start developing often over the age of 75. Just trouble with recent memory and not much else. And it can be confused with what looks like Alzheimer's disease. But sometimes, it's just due to this other pathology. But you can't detect that pathology yet in a living person so that you can't make a definitive diagnosis of that particular condition. I suspect that will change soon but not yet. That's one example. But there are other ones too, where there's rare causes of dementia that are not associated with a particular gene change that you would never know what it is until you do an autopsy sometimes.

NANCY LYNN KEACH: I'm going to switch gears because there are a few questions that are really-- I see all the time and are troubling. So Lori wrote, "I've been told that I am too young to be seen for this, even though I am having cognitive issues. Is there something that can be done to be seen?"

DR. DAVID HOLTZMAN: Well, I mean, if people are having cognitive issues at whatever age, they need to get seen. I mean, there's obviously lots of different things that can cause cognitive decline. Some are these degenerative diseases we're discussing, like Alzheimer's and related disorders. But there's also other brain diseases that need to be either ruled in or ruled out. So no matter what age you are-- there are rare situations where people even develop decline dementia due to Alzheimer's disease. And they're very rarely in their 20s. But 30s, 40s, it happens. And some of the other diseases as well can start quite early. So you're not too young if you think—

NANCY LYNN KEACH: It's never too early if you're having a problem. Yeah. I also wanted to read off this YouTube comment from Ken, "The system hasn't worked for me. High amyloid determined via spinal tap, tau is normal, appeared normal in multiple cognitive tests. But I have extreme memory problems."

And this is Anna Maria, "I'm fairly new to all this. What kind of doctor should my mom showing dementia signs see to address these issues and possibly testing to see what she has? The regular family doctor seemed dismissive."

So I think this is really common because the doctors really don't-- it's very hard for doctors to keep up with all these scientific advances because they're very busy. And we give a slide and email you all a list of resources at the end of every episode. But if someone's doctor is being dismissive, what are some resources, Dave, that they can go to?

DR. DAVID HOLTZMAN: Obviously, it depends on where they live. But I think if the possibility is that there might be the beginnings of a dementia, even if it's very, very subtle, like what was just described, I think the person does need to get referred to a specialist in this area. And as I said earlier, most commonly, it's a neurologist that has specialty area in memory and thinking disorders. Or it could be other people that have similar expertise. But if you don't get seen-- the only people that are really staying up on average with these problems are people that specialize in this. So I think, hopefully, you can-- I mean, where to find those people, It will depend on where you live and what centers are around.

One of the unfortunate things in our society right now in medicine is that there's not that many experts that see patients with this disorder that are really good at it. And it's not because it's not an important topic. Of course, it's super important. But just not that many physicians and neurologists go into this subspecialty clinically. But they're around. And especially with the new advent of these new disease modifying treatments, I think a lot of centers have really optimized their ability to get people in quicker than previously.

NANCY LYNN KEACH: Yeah, and that is another issue. And you find the neurologist you want to see and find out you have to wait nine months for an appointment. And that is a big issue. So I just want to confirm that if you get really frustrated, it's not you. There are a lot of problems in the system. There are some states that only have a handful of neurologists in the entire state. And it's very frustrating because, as we say, early diagnosis is so important. So don't stop trying and advocating for yourself. And that's also why I often will say, see if there's a clinical trial that you can volunteer for. And there are sites that will give you those. You can always write to us. We'll be happy to refer you because you will get seen if you are participating in research.

So I just want to note, we have 10 minutes left. So if anybody has a burning question and is hesitating to ask it-- oh, go ahead, Maureen.

AUDIENCE: Hi, thank you so much, Dr. Holtzman. Nancy Lynn, thanks so much. I have personal experience with this with my family. And also, I'm a filmmaker. And so right now, I'm working on a TV pilot that deals with memory care units. And so I guess my question is-- and this has been very helpful because I probably will need to go get tested at some point. We have vascular dementia and Alzheimer's in my family-- my parents and my brother and my sister. But would a skilled nursing facility have any impetus to test someone who might be in short-term care? Then maybe they need to be put in a memory care unit? What if they don't have any family? What happens there?

DR. DAVID HOLTZMAN: Well, I think no matter what stage of dementia somebody is at, whether it's the very earliest thing all the way to more severe, I think at some point, everybody deserves to get a diagnosis. Because even if they're-- these new treatments that just became available that can slow down the disease somewhat, those are only approved for people with very mild impairment.

AUDIENCE: Yeah, my brother started that.

DR. DAVID HOLTZMAN: OK. Let's say you are more impaired than that but have never received the right diagnosis, it's still really important to get diagnosed not just with whether you have dementia or not but what the physician thinks is causing the dementia. Because even if it's more advanced-- for example, somebody never had a brain scan to make sure they didn't have a bleeding or a tumor or something like that. It's still important to get a diagnosis.

AUDIENCE: Right. So the skilled nursing facility would be able to refer them to a doctor or a neurologist—

DR. DAVID HOLTZMAN: Oh, absolutely.

AUDIENCE: --if they didn't have family to advocate.

DR. DAVID HOLTZMAN: Right. And in some cases, a lot of times, people might be in a skilled nursing facility not because of a brain problem but something else that led them there.

AUDIENCE: Yeah.

DR. DAVID HOLTZMAN: And so yeah, no, I mean, absolutely, they deserve that.

AUDIENCE: Terrific, wonderful. Thank you.

NANCY LYNN KEACH: It's a great question, Maureen. We actually just did a program with an organization called the National Investment Center for Seniors Housing. And the chair of that board is a woman who says, the whole senior living, memory-assisted living, it's very problematic to keep staff that are knowledgeable. They have more than 100% staff turnover in a lot of these places. And so a lot of staff are not well trained enough in dementia care. So this is a big issue for our field as well that we're going to talk about.

AUDIENCE: Yeah, great, thank you.

NANCY LYNN KEACH: Anyone else that wants to get their question in real quick? I have a couple more I'm going to ask. But do raise your hand or write in the chat if you want to get something answered. Judy from Emory, Texas, "My husband was recently diagnosed. I believe the diagnosis was based on having APOE3 and APOE4 genes from blood test, plaque buildup, a PET scan, and mild cognitive decline, memory loss. Know there is currently no 100%." Basically, she's saying, is there some mix that's going to give you the most accurate diagnosis? And I know this is kind of repetitive.

DR. DAVID HOLTZMAN: Which mix of tests, you mean?

NANCY LYNN KEACH: Mix of tests. Or you did talk about blood tests, some having a higher accuracy than others. But is there a cocktail of tests that is going to get you the highest?

DR. DAVID HOLTZMAN: I would say-- yeah. So first, making sure that the clinical syndrome the person has is consistent, for example, with Alzheimer's versus something else. If it seems consistent even at the earliest stage and one of those other tests is positive, either the amyloid imaging, the spinal fluid test, or the blood test for p-tau217 or a combination of things, either any of those tests, that's a good one, with the clinical syndrome is probably as good as we can do right now.

NANCY LYNN KEACH: So now, I'm going to throw you a fun question. What comes next? What do you see in the future for detection with AI and linguistics and measuring gait?

DR. DAVID HOLTZMAN: Yeah, that's a good question. There's a number of things that I think will emerge. One is some of the other blood tests will detect some of the other pathologies in the brain that we're not detecting now. So I think that will be something that will come out in the next year or two years. So that's one thing. But then in terms of the other modalities of testing, there's a variety of work going on to try to look at smartphone testing remotely. Also, there's a research going on using AI to look at changes in voice over time, handwriting over time. So basically using a bunch of different modalities, not necessarily at one point to make the diagnosis, but see what changes over time. And if that helps in both assists in diagnosis but also gives an idea of what's going to happen to the person over time.

NANCY LYNN KEACH: So around nine years ago, I was with some scientists who were saying, we can detect psychosis through language patterns five years before symptoms will develop. But this is nine years ago. So what kind of a time frame would you predict for when we can use these types of behavioral observations to predict?

DR. DAVID HOLTZMAN: So really, I think the question is, when will any of these other modalities be clinically used and not just for research but clinically used? It's a little hard to predict. My best guess is that one of these-- I don't know which one. But one of them might be an adjunct within five years or so.

The other thing I didn't mention is that there are also ways to monitor sleep and circadian changes that might also be useful. But again, whether they become clinically available or not, I'm not sure when or which ones are going to be the most useful but probably by five years from now, I would expect.

NANCY LYNN KEACH: Yeah. And you're talking about sleep. It reminds me. We were talking earlier about risk factors that-- vision loss was just acknowledged as a risk factor, as is hearing loss. So there are lots of those types of interventions that could be made to reduce your risk.

And I just want to note for folks in the chat. Several people are writing back to Maureen's question about-- let me find the one I was just looking for. "I'm a speech therapist-- this is a YouTube comment from Libby-- in skilled nursing. And we can test and refer residents to neurologists and are often the ones who see people in the facility for cognitive deficits." So thank you for that, Libby.

Well, unfortunately, I could go on with this for another couple of hours. But I'm going to have to let you go, Dr. Holtzman. And I want to thank everybody for coming. And I especially want to thank Dr. Holtzman for giving his time. He really is one of the most respected, dearest leaders in the field. And you can tell that-- that is so not to embarrass you there, Dr. Holtzman. But not only because he is brilliant and has really made some pioneering discoveries, but he can describe the science in understandable terms and takes the time to do so. And I think we deeply appreciate that. He also serves as the chair of our Scientific Review Committee. So he also takes time and reviews all the grant proposals for new science that comes in. So we have the utmost respect and appreciation. And thank you so much for being here. And I hope you'll come back.

DR. DAVID HOLTZMAN: Thanks. I hope it was helpful.

NANCY LYNN KEACH: Very, very helpful. And all of you-- and you can bring those slides up. Thanks, Roger. If your question wasn't answered today or if there's other questions you want to think about later, please feel free to email them to us.

First of all, I'll just point out that we have several free publications that you can ask for Alzheimer's disease@brightfocus.org/zoomin. And the next slide. If you have suggestions for future topics, please email us, reply@brightfocus.org. And again, if you have questions that weren't answered today, you can email them there as well. And the next slide, please.

Next episode is right before Thanksgiving on Thursday, November 21st. And I think many of you know that we started a sub series on clinical research, where every other month, we take one trial. And we spend an hour talking about that trial. The last one we did was the START study and, before that, the HOPE study. And it's just a wonderful way to be able to slowly and clearly learn about trials. Right now, we're trying to do ones that are national and have a lot of sites all over the country so that people who want to can sign up and participate. And we have been having people sign up right during the episodes on the websites. So the next of those episodes is on December 5th. And we'll keep everyone alerted to those.

So again, I thank everybody so much for attending today and hope that we'll see you on November 21st. And have a great month.