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Alzheimer's Disease: Tools for Early Diagnosis

Announcer:
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Dr. Isaacson:
To achieve an earlier diagnosis and improve outcomes for our patients with Alzheimer's disease, it's critical that we recognize early symptoms and correctly use available assessment tools. Do you know what to look for and how to look for it?

This is CME on ReachMD, and I'm Dr Richard Isaacson.

Dr. Weiner:
I'm Michael Weiner.

Dr. Isaacson:
So we have a lot to cover in this activity, so let's get started. Dr. Weiner, great to be here with you today. Could you give us a brief overview of the various stages of Alzheimer's disease?

Dr. Weiner:
I'm happy to, Richard. First of all, we all should understand that Alzheimer's disease is a specific pathology that causes impairment leading to dementia. The pathology is amyloid plaques, tau tangles leading to neurodegeneration. The clinical stages of the disease are Alzheimer's disease, which occurs in normal people in which there's no symptoms. Then Alzheimer's disease begins to cause impairments which leads to the syndrome of mild cognitive impairment, which is a prodrome to development of dementia. And finally, there's the very well-known dementia, which is caused by Alzheimer's disease.

Dr. Isaacson:
Great, very clear. And you know, through medical school, we were taught one thing, and now as our diagnostic criteria have evolved, we've really honed in and really gotten so much more precise in our understanding, both of the clinical picture as well as the biomarker picture, as well as the neuroimaging picture which, really, you've been a pioneer at, you know, advancing our understanding. So that was a great overview.

Let's dive into the tools that are available to us. What's our best bet for screening and diagnosing our patients?

Dr. Weiner:
There are a variety of approaches. But in general, we ask the patients how they're doing. We ask family members or a close friend who has some opinion and observation on the patient and whether or not there's been a change in the patient's behavior or ability to function cognitively. And then we have neuropsychological tests, which can tell us whether or not the patient is in the normal range or whether there's a demonstrated impairment. A clinician needs to use all of that in order to determine whether someone is impaired.

Once that determination is made, then the next question is whether or not the impairment is due to Alzheimer's disease pathology or other types of pathology. As we've come to recognize the fact that Alzheimer's disease is caused by a specific pathology, that is amyloid, tau, and neurodegeneration, we are more and more starting to use biomarkers to detect amyloid, tau, and neurodegeneration. And those biomarkers include different types of scans, obtaining cerebrospinal fluid from a lumbar puncture, and, more recently, blood tests. And I think we're going to get into all of that as we keep talking.

Dr. Isaacson, can you tell us about using these tools on a daily basis in clinical practice?

Dr. Isaacson:
Sure. So our field has really advanced over the years. And while, you know, in medical school, we were taught that you can only make a diagnosis of Alzheimer's disease by using brain pathology after a person passes away on autopsy, now we have many tools that – in addition to a careful and comprehensive clinical history, so progressive short-term memory loss, other changes in cognitive or thinking skills, as well as possible changes in sleep and behavior. And that change is verified by someone who is with the patient, a loved one, a partner, someone that's noticed the change over time. We can then use tools like testing, not just neuropsychological testing, but spinal fluid testing, brain imaging tests, as well as the, you know, kind of evolving area blood tests that I'm very excited about in the coming months and years.

So in terms of the standard tools, well, again, start off with the clinical history. Progressive short-term memory loss, ask very key questions. Especially in a person with a family history of Alzheimer's disease, you can, you know, really try to get a reasonable degree of accuracy at diagnosis, clinical diagnosis, but then you need biomarkers and such to truly, you know, be certain.

So in clinical practice, we can do PET scans. There's 2 different types. So there's an FDG PET which looks at glucose uptake, and in different parts of the brain that are region-specific for decline in glucose metabolism; that can be suggestive of Alzheimer's disease – otherwise, other dementias, like frontotemporal dementia, depending on where that reduction in glucose metabolism is.

And then over the last decade or so we've now been able to use biomarker tests specifically for Alzheimer's. So we can label amyloid. There are now 3 FDA-approved amyloid-labeling agents. Now the good news is they are really helpful in a person that has a clinical history suggestive of Alzheimer's disease and progressive memory decline.

Over a year ago, actually, the first tau PET scan, tau-labeling agent, was approved. And now that's available. But again, it's, you know, not very common to use, it's costly, hasn't really been integrated into routine clinical practice.

The spinal fluid test is, I think, in some ways a preferred test by some practitioners because not only do you get amyloid, but you also get tau – phospho-tau and total tau – and that triplicate signature of the 3 biomarkers have a really strong predictive value in terms of what the actual pathology is and thus what the true diagnosis is for Alzheimer's disease.

I think where we're going is blood-based biomarkers, and I hope in the coming months and years, we'll get lots of news from tau, amyloid, neurofilament light, GFAP [glial fibrillary acidic protein]. So pros and cons with all the different options.

For those just tuning in, you're listening to CME on Reach MD. I'm Dr. Richard Isaacson. And here with me today is Dr. Michael Weiner. We're discussing tools for the early diagnosis of Alzheimer's disease.

Dr. Weiner:
What about in clinical trials, Dr. Isaacson? What tools are being used in that setting?

Dr. Isaacson:
So I think there's a reasonable amount of overlap. For example, in the Alzheimer's prevention trial, AHEAD 3-45, which is a very exciting study looking at people with preclinical disease, meaning people without symptoms or minimal cognitive changes, but basically people that have verified Alzheimer's pathology in the brain, amyloid as well as they'll check for tau.

So for example, AHEAD 3-45 does look at an amyloid PET scan. That study has also now most recently integrated the amyloid blood test that looks at, by mass spectroscopy, the amount of amyloid beta in the blood, and using a combination of the person's age and APOE4 gene status, can actually give a reasonable prediction – a strong prediction, actually, whether that person is amyloid positive or not. And then those people can then go on and get the PET scans. So these are necessary for inclusion. They're also used on a longitudinal basis to look for target engagement of the anti-amyloid or other agents that are used.

And then in terms of the cognitive assessments, there's a little different assessment, and this is a preclinical Alzheimer's Cognitive Composite, called the PACC. It's been used for quite a while along with Alzheimer's Prevention Cognitive Composite, which is also another scale. It's specifically used for people that don't have cognitive changes but are more sensitive to detect lower-than-expected cognitive performance on a specific cognitive test.

Depending on the different trial, for example, the Clarity AD trial does use some of the more traditional neuropsychological measures that are used for people that already have early mild Alzheimer's disease dementia, as well as mild cognitive impairment due to Alzheimer's disease. So these can include the clinical dementia rating scale, which is an excellent kind of real-world scale. It's called the Sum of Boxes, where you add up the different categories to understand the different levels of decline in different real-life areas, as well as the Alzheimer's Disease Composite score, the Alzheimer's Disease Assessment Scale Cognitive subset, as well as amyloid PET.

Across SCarlet RoAD and the GRADUATE 1 and 2 studies, and Trailblazer AD, different measures are used. Again, similar sort of approaches. CDR Sum of Box, florbetapir-PET, as well as the Integrated Alzheimer Disease Rating scale.

So I think the take-home point here is in clinical trials, there's a lot of different tools used. And it's just tricky, though, because how can we sometimes integrate these in clinical practice? And we can talk about that next.

Dr. Weiner:
I think that's a really important question. The tools that are used in clinical trials, for the most part, take quite a bit of time. And it's very unclear to me how most of these measures really could be incorporated into the busy practice. What is needed is the development of tools that can be used by physicians who are taking care of patients across the country that are well validated, that have demonstrated diagnostic accuracy, and are practical for people to employ in a clinical practice setting. We don't really have those.

It's possible that one approach to this is going to be the use of more and more online tools where people are asked a series of questions and possibly take some kind of online cognitive test as well.

But as we have more and more treatments – we already now have aducanumab, which is approved by the FDA, and hopefully there will be additional treatments that will be approved – and the more treatments that come into the arena, the greater the need there's going to be to have practical tools that physicians can use to make a diagnosis and determine whether or not their patients would benefit from therapy.

Dr. Isaacson:
Yeah, I couldn't agree with you more. It's hard enough to, you know, talk to patients for the amount of time that, you know, one needs to obtain a clinical history and then give counseling, give advice about how to manage the condition and whether you're prescribing drugs or lifestyle changes or you're trying to, you know, give support to the caregiver and educate the family about best practices in terms of caregiving support.

So there's almost never enough amount of time in routine clinical practice to even talk to the patient and their family, let alone having to do kind of, you know, broad-based assessments in terms of assessing cognitive domains, cognitive functions, doing the variety of quality-of-life scales, asking about neuropsychiatric symptoms. You know, and then aside from assessing them once, it's really critical to assess these measures over time to understand trajectory.

Dr. Weiner:
I think that computerized tests will be largely used as a screen. I think the blood tests, as they evolve, are going to be useful to determine whether or not people have abnormal pathology. But the blood tests are not going to indicate whether or not somebody is impaired or not. I think there's going to be an increasing role for nurses, neuropsychologists, physician's assistants, and other non-MD personnel who will get trained on doing some of the assessment procedures and potentially get trained to do more lumbar punctures, which is certainly a lower-cost way than PET scans to really establish a diagnosis of Alzheimer's disease pathology.

Dr. Isaacson:
I think my hope and my dream is that we can use these blood tests from amyloid and tau and neurofilament light and GFAP and whatever else. I hope that one day we can do sufficient research to understand that maybe we can track these markers. And just like we have the cholesterol test for the HDL and LDL, that one day this will be like a cholesterol test for the brain. And we can not only understand a person's trajectory, but maybe we can, you know, help predict and evaluate whether or not a person is responding to therapy in conjunction with the trajectory of neuropsychological decline and quality-of-life measures that we ask about.

Dr. Weiner:
As you mentioned, there are a number of so-called prevention trials, like the A4 study, the A45 study, and we can expect the pharmaceutical companies will be launching more and more so-called prevention trials once they demonstrate that their treatments are effective in people who are symptomatic. So the dream ultimately is that there could be mass screening of people, possibly with computerized testing, and then that leading to blood tests, which should not be too expensive. And if we could find a way to identify people at risk, they could be treated before they're symptomatic. And we could prevent Alzheimer's disease. I think that's the future. And there's a lot of evidence that this has got a lot of potential. So it's a very exciting area of medicine right now.

Dr. Isaacson:
That's great. Well, this has certainly been a fascinating conversation. But before we wrap up, Dr. Weiner, can you share one take-home message with our audience?

Dr. Weiner:
Not everybody who has cognitive impairment has Alzheimer's disease. So people who have cognitive problems or even developing dementia need a good workup to demonstrate whether or not they have Alzheimer's disease. And if they do, there's now an available treatment, or people should think about going into clinical trials.

Dr. Isaacson:
That's great. And what I would say is, there's a lot of hope now for Alzheimer's disease. And I think many people out there listening have kind of realized that we've, you know, had a lot of trial failures, and we've struggled. But I really think that we've learned so much from the past and can build a really successful future of Alzheimer's prevention and treatment. So I'm very excited about what will happen hopefully over the next several years.

So unfortunately, that's all the time we have for today. I want to thank our audience for listening and thank you, Dr. Michael Weiner, for joining me and for sharing all your valuable insights. It’s been a pleasure. Really great speaking with you today.

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