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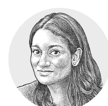
Why Doctors Can't Agree on How to Diagnose Alzheimer's

Divergent diagnostic criteria is raising concerns that some patients are being misdiagnosed and unnecessarily treated



By Sumathi Reddy Follow

Feb. 9, 2026 at 8:00 pm ET

A PET scan tests for amyloid, a protein in the brain that the Alzheimer's Association says defines the disease—but some doctors disagree. GETTY IMAGES

Imagine you're in your late 60s and are diagnosed with Alzheimer's disease.

You start planning the rest of your life: telling your spouse you may eventually become incapacitated; looking into long-term memory care; checking off as many bucket list items as you can.

Six months later, another neurologist finds the opposite: You don't have Alzheimer's and aren't at risk of developing it.

Divergent diagnoses for Alzheimer's are the result of different criteria for diagnosing the disease. Some doctors worry the differing approaches can result in patients going misdiagnosed, or worse, being prescribed medications with potential negative health effects.

The problem highlights a larger question: How should Alzheimer's disease be defined? Is it a biological disease based solely on the presence of brain proteins? Or is it a more complicated diagnosis that involves weighing risk and other factors?

The Alzheimer's Association 2024 criteria for diagnosis requires evidence of the brain protein amyloid. At the International Working Group, a global consortium of neurologists and researchers, its criteria requires three things: the presence of amyloid; tau, another biomarker of Alzheimer's disease; and cognitive symptoms.

Dr. Gayatri Devi, director of Park Avenue Neurology in New York City, is a neurologist who says over the past year she has seen an increasing number of patients who were told they had Alzheimer's disease when they didn't. One patient, a human-resources executive, had erroneously been diagnosed with Alzheimer's based on a faulty PET scan of his brain that had read positive for amyloid and his own fears of memory issues because he had missed an important meeting.

He was then started on monoclonal antibodies despite the fact that he didn't need them. A subsequent spinal tap showed no amyloid or tau. The patient didn't have Alzheimer's disease and isn't expected to develop it given his late-60s age and the fact that it takes years for amyloid plaques to build up, she says.

"That's why we need to be really cautious in giving someone a diagnosis," says Devi, who wrote a recent opinion piece published in the Annals of Internal Medicine outlining concerns about the different diagnostic criteria.

While the Alzheimer's Association criteria define the disease by amyloid pathology in the brain, it says testing and treatment should occur only if a patient has cognitive symptoms.

But doctors like Devi say this isn't always done in practice. Symptoms can be variable and subjective, and caused by other factors. Who, after all, doesn't feel like they have a lapse in

memory at times?

"Many people who are worried about prevention will go for testing," she says. "A lot of us have memory issues. We are all multitasking. So symptoms are difficult to define and difficult to self access."

Amyloid alone shouldn't define Alzheimer's disease, she says. Roughly 25% to 45% of seniors with no memory complaints have amyloid and most don't develop dementia, studies have found.

"Medicalizing everyone with amyloid in their 70s and 80s is a problem," she says. Monoclonal antibodies that are indicated for the early treatment of Alzheimer's disease, for example, have a risk of brain hemorrhages and bleeds.

The Alzheimer's Association says amyloid is a good proxy for tau. But the current tests for amyloid aren't sensitive enough to detect a few amyloid plaques in the brain.

So when a PET scan or spinal tap is positive for amyloid plaques, it almost always means there are also tau tangles present, says Dr. Clifford Jack, a radiologist and professor at Mayo Clinic in Rochester, Minn., and first author of the Association's criteria.

Symptoms of Alzheimer's disease typically don't surface until about 15 years after amyloid and tau is detectable in the brain, says Jack.

"So of course symptoms are a feature of the disease, but they don't define the presence of the disease," he says.

There are ongoing clinical trials to determine whether people with amyloid, but without cognitive symptoms, could benefit from taking monoclonal antibodies. Until those are done, people without symptoms shouldn't be tested for amyloid and tau and shouldn't be treated in the event they get a positive test, Jack says.

Some doctors say the different definitions of Alzheimer's disease are leading to estimates that are grossly inflated.

"You can't diagnose 47 million Americans with Alzheimer's disease," says Dr. Richard Isaacson, a preventive neurologist at the Institute for Neurodegenerative Diseases in Boca Raton, Fla., and Atria Health and Research Institute in New York. "These Americans have biological markers of

Alzheimer's disease risk starting in their brain and detectable in their blood. It doesn't mean all 47 million Americans have a stigmatizing diagnosis like Alzheimer's."

Isaacson strongly disagrees with the contention that Alzheimer's is a biological disease. Alzheimer's manifests in myriad ways, he says. Some patients may have tau with no amyloid. Others have amyloid without tau.

Just like having high cholesterol doesn't mean you will have a heart attack, having biomarkers like amyloid doesn't mean you're going to develop Alzheimer's disease, he says.

Dr. David Wolk, a neurologist and director of the University of Pennsylvania's Disease Research Center, says the debate comes down to semantics: having a disease versus being at risk of it.

Wolk says the danger of relying on cognitive symptoms and amyloid alone is that not all physicians will fully investigate cognitive symptoms that may have another cause.

It is common for someone, for example, to have cognitive symptoms caused by another source, such as vascular disease in the brain. But a person may also test positive for amyloid and be erroneously diagnosed with Alzheimer's disease.

"It wouldn't surprise me if there are some patients who are receiving these medicines and have Alzheimer's biology but it may not be a cause of their symptoms," he says.

Dr. Reisa Sperling is a neurology professor at Harvard Medical School who runs studies testing antiamyloid drugs in asymptomatic people with amyloid in their brain. She says the goal is early intervention.

She says the International Working Group's criteria requiring cognitive impairment to diagnose Alzheimer's disease is problematic, likening it to requiring someone with diabetes to wait until they have blindness or kidney failure to be diagnosed. "All disease begins before symptoms, and most diseases are better treated before people walk into your office with clear impairment," Sperling says.

Devi says the psychological impact of being told you have Alzheimer's when you don't is profound. Until the medical community can better agree on how to both diagnose early Alzheimer's disease and determine whether early treatment helps, patients should avoid unnecessary testing—especially with the advent of easily accessible blood tests.

Appeared in the February 19, 2026, print edition as 'Doctors Can't Agree on How To Diagnose Alzheimer's'.

Sumathi Reddy is the "Your Health" columnist at The Wall Street Journal, writing about all things health and medicine. Her columns cover everything from exercise and weight-loss drugs to cannabis and alcohol to infectious diseases and vaccines....

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