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## Alzheimer's Diagnostic Tests Inch Forward, but Treatments Are Still Lacking

Researchers are trying to develop ways to more quickly and accurately diagnose Alzheimer's, which might lead to better treatments and understanding in the future

February 27, 2015 | By Rebecca Harrington |

Kathy Stack's memory loss began with the little things: losing her wallet, taking a wrong turn, forgetting someone's name. In 2013 at the age of 68, she visited her neurologist, who sent her to a memory loss specialist. He told her she had a 50–50 chance of developing full-blown Alzheimer's disease within five years.

Two years later, Stack, who was the first female department director of community services for Saint Paul, Minn., has made lifestyle changes such as working out regularly and doing daily brain exercises to stave off the disease. She is prepared for what the next stages of Alzheimer's may bring, but says she has noticed her symptoms worsening.

More than five million people in the U.S. currently have Alzheimer's, and that number is increasing with the aging population. Clinical diagnoses from specialists can be accurate up to 90 percent of the time but currently the only way to confirm that an individual has the disease is to examine the brain after death. Researchers are working to develop tests that diagnose Alzheimer's earlier and more reliably. But with limited treatment options available, some experts worry that better tests may do more harm than good.



Clinical diagnoses from specialists can be accurate up to 90 percent of the time but the only way to absolutely verify that someone has Alzheimer's is to examine their brain in a postmortem autopsy. *Credit: NIH* 

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A number of diagnostic tests are now in various stages of development in the research pipeline. Researchers described one such test on Feb. 24 that will be presented at a meeting of the American Academy of Neurology in Washington, D.C. in April. It analyzes skin samples, using antibodies to look for proteins associated with Alzheimer's and Parkinson's diseases. Because skin and brain cells originate in the same place in the embryo, the researchers hypothesized that they'd find similar levels of tau—a protein that forms distinctive tangles in the brains of Alzheimer's patients—in both cell types. Early results suggest that Alzheimer's and Parkinson's gatients have elevated levels of tau in their skin. Lead investigator Ildefonso Rodriguez Leyva of the Autonomous University of San Luis Potosi in Mexico says they also found higher levels of the protein alpha-synuclein in the skin cells of Parkinson's patients but not those with Alzheimer's, which allowed them to distinguish one dementia from the other. The next step is to ramp up the study to include more subjects; these early results came from only 65 people. Rodriguez Leyva says he hopes they can offer the test within two years.

Other tests in development look for different possible markers of disease. Daniel Alkon of the Blanchette Rockefeller Neurosciences Institute in Morgantown, West Virginia and his group have developed a skin test that measures so-called protein kinase C, epsilon (PKCE) levels. PKCE promotes the growth of synapses in the brain and destroys tau protein. It decreases in patients with Alzheimer's. In clinical trials, Alkon and his group were able to predict which patients would get Alzheimer's more than 95 percent of the time by measuring PKCE levels in their skin cells. They validated their diagnoses with autopsies years later. But they only studied about 140 patients, and thus will require more findings in later-phase clinical trials. Alkon said he hopes to be able to offer the test to the public in about two years through what is known as a Clinical Laboratory Improvement Amendments-certified lab, and then will seek U.S. Food and Drug Administration approval after that.

The lone reliable genetic test for Alzheimer's can only identify the familial form of the disease, which accounts for about 5 percent of cases. This type of Alzheimer's arises from a mutation in one of three genes that encode proteins involved in the production and processing of amyloid-beta, which, when abnormal, can build up in the brain and form plaques characteristic of the disease. Another gene variant can warn of a predisposition to Alzheimer's, although having this mutation does not guarantee an individual will develop the disease. The single biggest risk factor is age.

In current diagnoses people usually go to the doctor only if they are concerned they have memory loss. To determine if the dementia is likely Alzheimer's a physician will typically administer memory tests, ask about family history and do a neurological exam. If physicians encounter an unusual type of dementia that they can't distinguish, says Keith Fargo, director of scientific programs for the Alzheimer's Association, they can give patients a PET (positron emission tomography) scan to detect amyloid plaques in the brain. The Alzheimer's Association, however, does not recommend it for all patients because amyloid buildup doesn't necessarily mean they have the disease. Patients could have plaques and no signs of the disease. It takes this suite of examinations to reach the final diagnosis, which is partly what is motivating researchers to develop one single test.

Seeking an early diagnosis can rule out other causes of dementia such as Parkinson's, multi-infarct dementia or vitamin B deficiencies, some of which are treatable. Edward J. Goetzl, a senior clinical investigator at the National Institute on Aging who developed a promising blood test that will soon be available via a CLIA-certified lab, says early diagnoses could lead to better results from existing drugs. By the time many patients start taking drugs aimed at reducing the damage the disease has caused, he says, it's often too late for therapeutics to have much effect. "I think there are hundreds of great drugs out there," Goetzl says, "but by the time they start them, the cells are dead."

Finding a test that can diagnose Alzheimer's sooner could eventually mean that patients receive the news years before severe symptoms set in. At the very worst, Goetzl says, early diagnosis could mean having to retire or lose freedoms such as car privileges. It can also lead to depression, however. "Diagnosing before [symptoms worsen] presents all kinds of ethical and personal challenges that, in my opinion, we aren't really prepared to deal with," Alkon says. "In the absence of a definitive curative therapy, getting to know that you may get this disease 20 years from now might not do you any good, in fact it may cause you harm."

But in a 2014 GE Healthcare survey (pdf) of 10,000 people worldwide, nearly three quarters of respondents said they would want to

know if they had a neurological disorder, even if it had no cure. In this age when so much health information is readily available, from genetic sequencing to early disease diagnoses, it now seems that knowing what could come is preferable to finding out when it happens.

For Stack, the diagnosis was a chance to make decisions before she could not make them for herself. In the weeks following her diagnosis she met with her lawyer, financial planner and visited long-term care facilities. "It's not as dire as it sounded two years ago when [my doctor] just kind of laid it out for me. I didn't think 50–50 sounded like good odds at the time," Stack says. "I think that we are slowing down the progression of the disease, so I can be hopeful."

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