Medical News

# Alzheimer Disease Blood Test Cleared for Primary Care, but Questions Remain About Its Use

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General internist Barak Gaster, MD, has spent the last 8 years focused on the management of dementia in the primary care setting. He directs the Cognition in Primary Care program at the University of Washington and is invited to speak on the topic a couple of times a month around the country.

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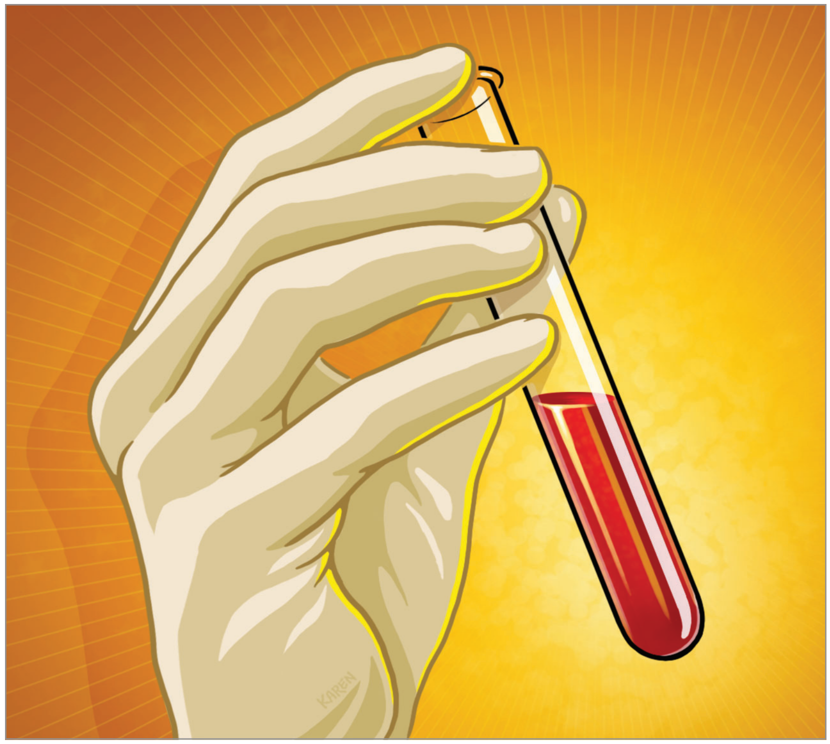
He says the number one question he's been fielding from primary care colleagues is whether they should be ordering blood tests for Alzheimer disease biomarkers for their patients. "They're saying, 'What does this test mean?'"

The question has become even more pressing since the US Food and Drug Administration (FDA) in October cleared the first such blood test for use in primary care. Roche developed the test, part of the company's Elecsys immunoassay product line, with Eli Lilly, maker of donanemab (Kisunla), 1 of 2 recently approved Alzheimer disease treatments that are driving the market for blood tests to detect Alzheimer pathology.

Although the Elecsys test is the first greenlighted by the FDA for use in primary care, it is not the first blood test for Alzheimer disease biomarkers to hit the market. In May, the FDA cleared Fujirebio's Lumipulse test for use by dementia specialists. Both FDA-cleared tests are available only by prescription and are intended only for evaluating patients with mild cognitive impairment or early dementia, not those with normal cognition.

In addition, several Alzheimer disease blood biomarker tests are on the market as "laboratory developed" tests, over which the FDA has exercised enforcement discretion. Such tests can be sold legally, but they haven't been reviewed by the FDA. At least 2 websites are marketing these Alzheimer blood biomarker tests directly to consumers with normal cognition, claiming that they can help such individuals "learn [their] Alzheimer's disease risk early" or "detect dementia 20 years before symptoms start."



However, experts say such claims get ahead of the science, raising concerns that physicians who have little training in evaluating or treating patients for cognitive impairment may misuse Alzheimer blood biomarker tests.

These tests are useful in helping to determine whether patients with cognitive impairment or early dementia might be eligible for new monoclonal antibody therapies, namely donanemab and lecanemab (Leqembi), for treating Alzheimer disease. But, despite the direct-to-consumer companies' claims, the tests can't yet predict whether people with normal cognition are destined to develop Alzheimer disease.

"[I]t is important to understand this test is designed to rule out the presence of amyloid plaques," Joanne Pike, DrPH, Alzheimer's Association president and chief executive officer, noted in a press release about the new Roche blood biomarker test. "It is not a test that will give an Alzheimer's disease diagnosis, nor is it a standalone tool for detection."

## From Brain to Blood

Until recent years, Alzheimer disease could be confirmed only by autopsy, when the brains of individuals with clinical dementia were found to have the pathological hallmarks of amyloid-β plaque and neurofibrillary tangles composed of abnormally phosphorylated tau (p-tau).

Since then, 2 methods have been developed for detecting Alzheimer disease pathology in patients living with clinical dementia symptoms. One involves brain imaging with amyloid positron emission tomographic (PET) scans, and the other involves a lumbar puncture to extract a small amount of cerebrospinal fluid for analysis. But these tools are expensive, not easily accessible to all patients, and, in the case of lumbar punctures, highly invasive.

The latest development has been tests to detect amyloid, p-tau, or both in blood, which are correlated with the presence or absence of plaque in the brain. The 2 blood tests cleared by the FDA require a prescription and are indicated only for adults 55 years or older.

The Lumipulse test measures the ratio of p-tau217 to β-Amyloid 1-42 in the blood. The test has 2 cut points: those who score above the higher cut point have Alzheimer disease pathology; those who score below the lower cut point, don't. Results between the 2 cut points are indeterminate.

The Elecsys test checks for levels of p-tau181 in the blood and, unlike the Lumipulse test, is designed only to rule out Alzheimer disease, not also to rule it in.

Studies have shown that p-tau217 is a more reliable biomarker than p-tau181, according to neurologist Fanny Elahi, MD, PhD, director of biomarkers and genomics research at the Icahn School of Medicine's Alzheimer's Disease Research Center at Mount Sinai. "The difference is not massive, but we've abandoned 181," she said.

Roche's more invasive test to assess Alzheimer disease biomarkers in cerebrospinal fluid also uses p-tau181, which previously was the most validated biomarker, said Maria-Magdalena Patru, MD, PhD, scientific partner, neurology, at Roche Diagnostics US. Patru acknowledged that p-tau217 appears to have better diagnostic accuracy than p-tau181 and said that Roche expects to soon have a p-tau217 blood biomarker test on the market. Whether it will be intended for use in primary care or in specialty care cannot be determined until regulatory clearance, a Roche spokeswoman said.

The performance of Roche's p-tau181 blood biomarker test was evaluated in a multicenter clinical trial with more than 300 participants, according to the FDA's decision summary. The test's negative predictive value (NPV)—the probability that a person with a negative result truly doesn't have Alzheimer pathology—was about 98% in an early disease, low-prevalence population such as that found in a primary care setting.

But the test's positive predictive value (PPV)—the probability that a person with a positive result truly has the disease—was only about 22%. A test's PPV typically is lower than its NPV in a population in which the disease isn't common, as is the case with primary care patients and Alzheimer disease. "In primary care, we believe a rule-out test makes the most sense," Patru said.

If they are interested in antiamyloid therapy, patients whose blood test result is positive must undergo a PET amyloid scan or a lumbar puncture to determine whether they indeed have plaque in the brain, Patru said.

## Why Test?

Cognitively normal people who keep losing their keys or their phone aren't the target market for her company's blood test, which primary care physicians will be able to begin ordering in December, Patru said.

"A patient who doesn't have Alzheimer's is able to retrace their steps" and eventually find their misplaced belonging, she explained.

Although the main use of blood biomarker tests has been as a first step in determining eligibility for antiamyloid therapy, even patients who aren't interested in the treatments have a reason to test, Patru said. "Let's not forget first and foremost, if someone has cognitive impairment, they want to know why. Do I have Alzheimer's? I want to put things in order."

At present, though, distinguishing between Alzheimer disease or another irreversible cause of dementia probably doesn't make much difference in planning for what's to come among people with cognitive impairment who aren't seeking antiamyloid therapy, Elahi noted.

"We actually fall short of prognosticating how fast someone will decline and what the future of their disease will look like," she said. "My patients are always asking me: 'How long am I going to have with my grandchildren?' I say, 'I'm with you—it's quite disheartening that we're not able to predict yet.'"

Although some companies are marketing Alzheimer blood biomarker tests to cognitively normal people, testing such individuals, whether they have a family history of the disease or not, "at this point shouldn't be done," Gaster said. As Elahi added, "We don't fully understand the predictive ability of these biomarkers for someone who is completely asymptomatic."

In the coming months, the discussion about whom to test could evolve, though, depending on the results of Eisai's phase 3 clinical trial of its drug lecanemab in people with early Alzheimer disease as well as those with what has come to be called *preclinical* Alzheimer disease. The latter group consists of individuals with normal cognition but elevated amyloid as determined by blood or cerebrospinal biomarkers or PET scans, some of whom will never go on to develop clinical Alzheimer disease.

However, a widely used drug that could have dramatically affected the discussion about testing for Alzheimer disease blood biomarkers proved disappointing in 2 recent phase 3 trials. Semaglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, already is approved to treat type 2 diabetes and overweight and obesity. But maker Novo Nordisk announced on November 24 that although treatment with oral semaglutide improved Alzheimer disease-related biomarkers in both trials, that did not translate into a delay of disease progression.

## Negative? Positive? Now What?

Patru noted that "it is important for the health care provider to discuss the test with the patient and the expectation this patient has for follow-up."

And yet, primary care physicians lack clinical practice guidelines on how to use Alzheimer biomarker blood tests and what to say to patients about them.

The Alzheimer's Association released guidelines this past summer for the use of blood biomarker tests, but they apply to testing in the specialty care setting, not primary care.

"We started with guidelines for use in cognitively impaired people in specialty care settings mostly because that's where the majority of the evidence was," guideline committee cochair Heather Whitson, MD, MHS, codirector of the Duke–UNC Alzheimer's Disease Research Center, explained in an email.

"But," she continued, "we always saw that as the initial step. I hope that we will update those guidelines as new evidence emerges and also create guidelines for different populations that will have different pretest probabilities of brain amyloid (such as primary care)."

For now, though, primary care physicians are flying blind. "Physicians still don't know what to say," Gaster said. "This is like a brave new world."

Because primary care physicians can order the Roche test, though, "it's kind of implied that you can explain the results to your patient," said Corey Bolton, PysD, a Vanderbilt University clinical neuropsychologist who was the lead author of a recent review article about disclosing blood-based biomarker results in primary care. "Most primary care doctors are probably not there now. They haven't received the training."

And yet, as Bolton and his coauthors noted in their review article, primary care physicians will be tapped to help meet the expected increased demand for testing as Alzheimer disease awareness and treatments grow.

"There has to be a strategy in place: What do we do with people screening negative but they still have memory problems?" Bolton said. "You have to answer the question of what's going on with them."

Positive results may be even more challenging to deal with than negative results, considering that the PPV in primary care can be so low that many positives are bound to be false.

"A positive test result may not be consistent with a positive amyloid PET scan result," according to the FDA's decision summary for the Roche test. "Patients with an initial positive result should be further investigated to determine whether the amyloid pathology can be a cause of cognitive impairment."

Patients' positive results are likely to spur "tons of fears or questions" their primary care physician is not equipped to answer, Bolton said. "Then they have to get referred to a specialist and wait 6 months until they can be seen." ■

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**Note:** Source references are available through embedded hyperlinks in the article text online.