THE NEW OLD AGE

Apparently Healthy, but Diagnosed With Alzheimer's?

New criteria could lead to a diagnosis on the basis of a simple blood test, even in the absence of obvious symptoms.

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Determining whether someone has Alzheimer's disease usually requires an extended diagnostic process. A doctor takes a patient's medical history, discusses symptoms, administers verbal and visual cognitive tests.

The patient may undergo a PET scan, an M.R.I. or a spinal tap — tests that detect the presence of two proteins in the brain, amyloid plaques and tau tangles, both associated with Alzheimer's.

All of that could change dramatically if new criteria proposed by an Alzheimer's Association working group are widely adopted.

Its final recommendations, expected later this year, will accelerate a shift that is already underway: from defining the disease by symptoms and behavior to defining it purely biologically — with biomarkers, substances in the body that indicate disease.

The draft guidelines, Revised Criteria for Diagnosis and Staging of Alzheimer's Disease, call for a simpler approach. That could mean a blood test to indicate the presence of amyloid. Such tests are already available in some clinics and doctors' offices.

"Someone who has biomarker evidence of amyloid in the brain has the disease, whether they're symptomatic or not," said Dr. Clifford R. Jack Jr., the chair of the working group and an Alzheimer's researcher at the Mayo Clinic.

"The pathology exists for years before symptom onset," he added. "That's the science. It's irrefutable."

He and his colleagues on the panel do not recommend testing people who have no symptoms of cognitive decline. But skeptics predict that's likely to happen nonetheless. If so, a sizable proportion would test positive for amyloid and would therefore be diagnosed with Alzheimer's.

A 2015 Dutch study estimated that more than 10 percent of cognitively normal 50-year-olds would test positive, as would almost 16 percent of 60-year-olds and 23 percent of 70-year-olds. Most of those individuals would never develop dementia.

A number of experts and interested parties remain unpersuaded by the argument for turning to biomarkers alone, however. The American Geriatrics Society has called the proposed criteria "premature" — and has noted the high proportion of panel members with ties to the pharmaceutical and biotechnology industries, creating potential conflicts of interest.

"This is jumping the gun by at least five to 10 years," said Dr. Eric Widera, a geriatrician at the University of California, San Francisco, and the author of a sharply critical editorial in The Journal of the American Geriatrics Society.

Some background: The panel undertook the effort only five years after issuing the last guidelines for diagnosis, because “two big events really mandated a revision,” Dr. Jack said.

First, the best of the amyloid blood tests proved to be highly accurate, less invasive than spinal taps and far less expensive than brain scans. In addition, aducanumab (brand name: Aduhelm) and lecanemab (Leqembi), two drugs that remove amyloid from the brain, received regulatory approval, though not without intense controversy.

Studies showed that the drugs had a modest but statistically significant ability to slow the progression of symptoms over 18 months in those with mild cognitive impairment or mild Alzheimer’s disease. (The drugmaker Biogen is withdrawing aducanumab, but other amyloid-reducing drugs are in the pipeline.)

Are those developments enough to warrant the possibility of diagnosing healthy people with an irreversible disease, based on a blood test detecting amyloid? Some doctors are already fielding such requests.

Diagnosing Alzheimer’s before symptoms emerge could allow yet-to-be-developed treatments to prevent the memory loss, diminished judgment and eventual dependence the disease causes. Doctors diagnose many diseases, including diabetes and cancer, with tests in asymptomatic people.

But how many of those with amyloid in the brain (most of whom will also have tau deposits) will eventually develop dementia? “The answer, unfortunately, is it depends,” Dr. Jack said.

The Mayo Clinic Study of Aging followed nearly 5,000 cognitively normal older adults in one Minnesota county for an average of 9.4 years. It found high rates of dementia among those who carried the APOE4 gene, which is associated with an increased risk of Alzheimer’s.

For those who were 65 and had high levels of amyloid, the estimated lifetime risk of dementia reached 74 percent for women and 62 percent for men.

But only 15 to 25 percent of people carry that gene, according to the National Institute on Aging. Among participants who did not, both men and women at 65 had an estimated lifetime dementia risk of about 55 percent with high amyloid levels and 36 percent with moderate levels.

“Because death rates are high in older people, many will die before they develop dementia,” Dr. Jack said.

Dr. Jason Karlawish, a geriatrician and co-director of the Penn Memory Center in Philadelphia, said he considers amyloid “a risk factor, in the way smoking is a risk factor for cancer.

“But I think the evidence remains not yet clear and convincing that amyloid alone defines Alzheimer’s disease.”

Two major studies of amyloid-reducing drugs in cognitively normal people, expected to conclude in 2027 and 2029, might provide such evidence if they are able to demonstrate that removing amyloid prevents, arrests or reverses cognitive decline in that age group.

For now, the proposed guidelines “are just not ready for clinical practice,” Dr. Karlawish said.

As for the working group, about a third of the 22 members are employed by companies developing drugs and diagnostics, their disclosures show. Roughly another third disclose research grants or contracts, consulting fees, honorariums or other payments from industry sources.

“They will directly benefit from this change,” Dr. Widera said. He pointed to estimates that 40 million cognitively normal Americans could test positive for amyloid, be diagnosed with Alzheimer’s disease and possibly begin off-label drug regimens, despite no evidence to date that the medications are effective in asymptomatic people.

“These are not benign drugs,” Dr. Widera added. “You’ll be on these drugs for the rest of your life — like a statin, but a lot more expensive and a lot more dangerous.” Aducanumab and lecanemab can cause brain bleeds and shrink brain volume, side effects that are not uncommon.

Dr. Widera further criticized the working group’s proposal for not discussing the harms of the new criteria — including needlessly terrifying people unlikely to develop dementia and potentially causing discrimination in employment and insurance.

Dr. Jack, who has no reported conflicts of interest, defended his working group. “The members are committed to accurately reflecting what the current

science says," he said. "There was no consideration of commercial gain. Everyone was focused on what's best for patients."

Numerous studies have found, however, that industry payments and sponsorship, even for inexpensive meals, have measurable influence. They are associated with doctors being more likely to prescribe promoted drugs, and with more favorable research results when manufacturers sponsor studies of drugs and medical devices.

Many patient advocacy groups, including the Alzheimer's Association, also have industry ties.

Often, redefining diseases or revising guidelines means reducing thresholds and broadening classifications, sometimes called "diagnosis creep." The thresholds for high blood pressure and high cholesterol are lower now than in previous years, for example. New precursor conditions like prediabetes also expand the number of people defined as having a disease.

With amyloid testing as the criterion, "there will be a new pandemic of Alzheimer's disease," Dr. Widera predicted. "There will be a big push for early detection."

Some of that push may come from patients themselves. "We are in an information age where people are interested in knowing more about their current and future health," said Dr. Gil Rabinovici, a neurologist who directs the Alzheimer's Disease Research Center at the University of California, San Francisco.

An early diagnosis of Alzheimer's disease might prompt lifestyle changes — quitting smoking, exercising, improving diet — that could still have "a protective effect," he said.

"I personally would not elect to know if I had plaques in my brain," he added. And he would not prescribe amyloid drugs to patients without symptoms, he said, until further research showed effectiveness in that cohort.

Still, "we've graduated from the notion that the doctor determines who learns what," he said, adding that after thorough counseling, "if I'm convinced I'm not going to harm them and I feel they understand the information they're going to get, I'm not going to decline to offer them a test."

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