



Alzheimer's Disease, Biomarkers, and mAbs — What Does Primary Care Need?

Nathaniel A. Chin, M.D., and Claire M. Erickson, Ph.D., M.P.A.

A computer notification interrupts a memory specialist's end-of-day note writing. A patient's test result has just been posted. The patient, Ms. J., was recently diagnosed with mild

cognitive impairment. Desperately hoping to be eligible for the new monoclonal antibody (mAb) therapy for Alzheimer's disease, she sought a blood test for p-tau217.¹ Her specialist, Dr. A., knows that Ms. J. was notified of the posted result and sees that she's already viewed it. Trying to avert alarm, he calls her to explain.

When Dr. A. asks Ms. J. and her husband, "What questions do you have?" 45 minutes of rapid-fire questions ensue. Dr. A. defines and differentiates mild cognitive impairment, dementia, and Alzheimer's disease to ground the discussion. The couple asks whether the test could be wrong and, if it's correct, what it means for their future. They ask how soon Ms. J. can get treatment. There's not

enough time to respond to all their questions, in part because there are no precise or simple answers.

Trying to focus on the blood test, Dr. A. explains that the "elevated" amyloid result confirms the suspicion that Alzheimer's is a cause of Ms. J.'s symptoms. He avoids the term "positive": it's confusing and imprecise, conveying the wrong message. Although this new result is important, Ms. J.'s depression, anticholinergic medications, and sleep apnea may also be contributing to her symptoms. Dr. A. adds that she may be eligible for mAb therapy, but a separate evaluation is needed.

This scenario may soon be typical for clinical care of memory disorders. Until recently, diagnoses and treatment discussions

involved less precise tools and fewer options. Testing included basic laboratory tests, structural head imaging, and an objective cognitive examination. Physicians relied on clinical judgment, not Alzheimer's-specific biomarkers, to determine the likely cause. Regardless of the testing conducted or its results, donepezil and memantine were the only treatment options. But discussions with patients and families were rarely easy. The issues are nuanced, and families often inquire about experimental treatments they've heard about in the lay media. New mAb therapies and blood-based biomarkers now further complicate the conversation. Results of biomarker tests can be ambiguous, and yet these tools determine whether mAb therapies are even a possibility for a given patient. So more time is required for a clinician to explain results and discuss next steps.

Though insurers generally will not cover blood tests for Alzhei-

mer's biomarkers, which currently lack Food and Drug Administration approval, these obstacles may soon be removed. But the U.S. health care system remains ill equipped to navigate discussions about the test results and treatments, lacking the time, staff, and expertise for adequately explaining results and answering patients' questions. It can take a memory specialist hours of in-clinic and phone conversations to provide one patient with answers about a diagnosis and test result, and these conversations may create additional uncertainty about treatments and other considerations (mAb eligibility, risk for amyloid-related imaging abnormalities, apolipoprotein E testing, serial brain scans, costs, etc.). In Ms. J.'s case, Dr. A. might not have the necessary time, and a primary care physician (PCP) would have even greater time constraints.

Indeed, diagnosing and discussing neurodegenerative diseases require training and time that few, if any, PCPs have. Memory clinics often operate on a collaborative care model, which may involve a neuropsychologist, a social worker, a nurse practitioner, and a nurse alongside a physician specialist. Initial assessments can take 2 to 3 hours, and an additional hour of follow-up care may be required every few months. Nurses and social workers spend countless hours on the phone with patients and families in between visits to guide the care that is left unaddressed during visits. The hypothetical call with Ms. J. hints at the innumerable unbilled hours that may be spent on each patient. As more people gain access to and seek out Alzheimer's biomarker testing, how will memory clinics and specialists keep up? More important, how can this

process be translated for primary care, which must serve five times as many patients per day?

The short answer is that it can't, though many observers believe that diagnosing Alzheimer's disease will soon have to happen in primary care. After all, most patients have better access to primary care than to specialty care, and the number of people with dementia is increasing. By 2050, more than 12.7 million Americans may be living with Alzheimer's disease.² Memory specialists and clinics do not have the capacity to meet their needs alone. Although biomarker testing and mAb therapy may more appropriately be offered in specialty care settings, PCPs can aid in the detection and diagnosis of dementia, helping to connect patients with much-needed resources. Already, the majority of diagnoses are made by physicians who are not dementia care specialists.³

Yet many PCPs report having low confidence in their ability to make and communicate a dementia-related diagnosis. Reported barriers include lack of training and perceptions that assigning a diagnosis is not beneficial.⁴ The dissonance between widespread expectations about new roles in dementia diagnosis and PCPs' own beliefs will have to be reconciled before the use of biomarkers becomes mainstream, which will further escalate the demand for overstretched clinicians' time. PCPs are a key to building a "dementia-capable" health care system, but they need to be appropriately trained and supported if they are to aid in the early identification and diagnosis of cognitive impairment.

Building PCPs' confidence in diagnosing mild cognitive impairment and dementia in general is a necessary and feasible step.⁵ This

aim can be partially accomplished with specific continuing medical education that could be required by state medical boards. Such training could be pragmatic, helping PCPs comfortably diagnose the syndromes of mild cognitive impairment and dementia and then identify patients who would benefit from referrals to memory clinics and specialists. Specialists can diagnose complex cases, identify specific brain diseases (Alzheimer's, Lewy body disease, cerebrovascular, and frontotemporal), determine patients' eligibility for mAb treatment, and manage the care of patients who receive new therapies.

In addition to training, PCPs need more time with patients with memory problems, as well as sufficient staff to coordinate their care. These needs generally cannot be met in our current health care system. Infrastructural changes enabling the implementation of multidisciplinary care models would greatly benefit primary care. Appropriately integrated care would involve more social workers and nurses, allowing PCPs to take more time with each patient. But though that ideal is worth advocating for in the long run, realistic changes to the current health care system are needed today. New payment models may be one avenue worth pursuing. For example, the Centers for Medicare and Medicaid Services is currently testing the Guiding an Improved Dementia Experience (GUIDE) Model, which financially supports a team-based approach to dementia care. GUIDE's aim is to improve services in dementia care and address the needs of unpaid caregivers, partly by adding a patient care navigator to the standard clinical team.

Collective efforts by institutional, state, and federal stakeholders are needed to equip PCPs to provide memory care. If society wants earlier, more reliable diagnoses and access to advanced disease-modifying therapies, then a sincere investment in primary care is required. Alzheimer's biomarker testing and new therapies are

 **An audio interview with Nathaniel Chin is available at NEJM.org**



poised to improve the diagnostic process and treatment, but without infrastructural change, the prom-

ise of these medical advances will fail to materialize.

Disclosure forms provided by the authors are available at NEJM.org.

From the Department of Medicine, Division of Geriatrics and Gerontology, University of Wisconsin School of Medicine and Public Health, Madison (N.A.C.); and the Department of Medical Ethics and Health Policy, University of Pennsylvania Perelman School of Medicine, Philadelphia (C.M.E.).

This article was published on June 22, 2024, at NEJM.org.

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DOI: 10.1056/NEJMp2401854

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State and Local Climate Litigation for Protecting Public Health

Avery E. Emery, B.S., and Daniel G. Aaron, M.D., J.D.

Climate change is a public health crisis. Communities are struggling to shoulder the costs of establishing critical public health infrastructure to mitigate the physical and mental health effects of rising temperatures, poor air quality, and extreme weather events. Meanwhile, the U.S. Supreme Court has limited the ability of federal regulators to implement public health measures, including those aimed at addressing climate change. In the absence of a comprehensive national approach to confronting the climate crisis, various states and local governments have sought to use litigation to pass many of the costs of addressing the public health effects of climate change on to the oil companies that they allege have contributed to this crisis. Although the progress of these lawsuits has repeatedly stalled, a recent settlement on the eve of a trial in a related case brought by Cameron Parish, Louisiana — seeking as much as \$7 billion in damages from 26 companies in

the oil and natural-gas industries — could be a bellwether for the efficacy of lawsuits against oil companies targeted at remediating the costs associated with climate change, including public health costs.

As global mean temperatures continue to rise because of emissions of greenhouse gases, severe weather events are expected to occur more often, cause greater damage, and kill, injure, or displace increasing numbers of people.¹ Beyond exacerbating hurricanes, wildfires, and droughts, climate change will most likely make illness and deaths related to heat, air pollution, and undernutrition more common.¹ Even according to conservative predictions, under which greenhouse-gas emissions peak around 2040, the United States will face an enormous burden of premature death and billions of dollars of health-related costs each year because of extreme temperatures, infectious diseases, and air pollution.²

The health effects of climate

change in the United States won't be evenly borne by all communities. Marginalized racial and ethnic communities and low-income communities have been disproportionately affected by climate change and air pollution.³ A long history of structural racism has resulted in marginalized groups, particularly Black people, being more likely than White people to live near major sources of pollution and in neighborhoods that have few green spaces and tend to be heat islands.³

Communities increasingly need to consider the effects of climate change when making decisions about public health infrastructure. The U.S. Global Change Research Program has highlighted the benefits associated with making health care infrastructure more resilient to the effects of climate change. For example, the Nicklaus Children's Hospital in Miami spent \$11.3 million to make critical updates, including building a shell intended to allow the hospital to withstand Category 4 hurricanes.²