severe aortic stenosis at extreme risk for surgery. *J Am Coll Cardiol*. 2014;63(19):1972-1981. doi:10.1016/j.jacc.2014.02.556

8. Adams DH, Popma JJ, Reardon MJ, et al; US CoreValve Clinical Investigators. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med*. 2014;370(19):1790-1798. doi:10.1056/NEJMoa1400590

9. Leon MB, Smith CR, Mack MJ, et al; PARTNER 2 Investigators. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *N Engl J Med*. 2016;374(17):1609-1620. doi:10.1056/NEJMoa1514616

10. Reardon MJ, Van Mieghem NM, Popma JJ, et al; SURTAVI Investigators. Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. *N Engl J Med*. 2017;376(14):1321-1331. doi:10.1056/NEJMoa1700456

11. Wu CM, McLaughlin K, Lorenzetti DL, Hill MD, Manns BJ, Ghali WA. Early risk of stroke after transient ischemic attack: a systematic review and meta-analysis. *Arch Intern Med*. 2007;167(22):2417-2422. doi:10.1001/archinte.167.22.2417

12. Messé SR, Acker MA, Kasner SE, et al; Determining Neurologic Outcomes from Valve Operations (DeNOVO) Investigators. Stroke after aortic valve surgery: results from a prospective cohort. *Circulation*. 2014;129(22):2253-2261. doi:10.1161/CIRCULATIONAHA.113.005084

13. Cho SM, Deshpande A, Pasupuleti V, Hernandez AV, Uchino K. Radiographic and clinical brain infarcts in cardiac and diagnostic procedures: a systematic review and meta-analysis. *Stroke*. 2017;48(10):2753-2759. doi:10.1161/STROKEAHA.117.017541

14. Kapadia SR, Kodali S, Makkar R, et al; SENTINEL Trial Investigators. Protection against cerebral embolism during transcatheter aortic valve replacement. *J Am Coll Cardiol*. 2017;69(4):367-377. doi:10.1016/j.jacc.2016.10.023

15. Mack MJ, Acker MA, Gelijns AC, et al; Cardiothoracic Surgical Trials Network (CTSN). Effect of cerebral embolic protection devices on CNS infarction in surgical aortic valve replacement: a randomized clinical trial. *JAMA*. 2017;318(6):536-547. doi:10.1001/jama.2017.9479

16. Giovannetti T, Price CC, Fanning M, et al; DENOVO Investigators. Cognition and cerebral infarction in older adults after surgical aortic valve replacement. *Ann Thorac Surg*. 2019;107(3):787-794. doi:10.1016/j.athoracsur.2018.09.057

17. Carroll JD, Vemulapalli S, Dai D, et al. Procedural experience for transcatheter aortic valve replacement and relation to outcomes: the STS/ACC TVT Registry. *J Am Coll Cardiol*. 2017;70(1):29-41. doi:10.1016/j.jacc.2017.04.056

18. LaPar DJ, Ghanta RK, Kern JA, et al; Investigators for the Virginia Cardiac Surgery Quality Initiative. Hospital variation in mortality from cardiac arrest after cardiac surgery: an opportunity for improvement? *Ann Thorac Surg*. 2014;98(2):534-539. doi:10.1016/j.athoracsur.2014.03.030

19. Salazar JD, Wityk RJ, Grega MA, et al. Stroke after cardiac surgery: short- and long-term outcomes. *Ann Thorac Surg*. 2001;72(4):1195-1201. doi:10.1016/S0003-4975(01)02929-0

20. Bevan GH, Zidar DA, Josephson RA, Al-Kindi SG. Mortality due to aortic stenosis in the United States, 2008-2017. *JAMA*. 2019;321(22):2236-2238. doi:10.1001/jama.2019.6292

Putting the New Alzheimer Disease Amyloid, Tau, Neurodegeneration (AT[N]) Diagnostic System to the Test

David Wolk, MD; Stephen Salloway, MD, MS; Brad Dickerson, MD

The field of neurodegenerative dementias, particularly Alzheimer disease (AD), has been limited by challenges in accurate diagnosis, but has recently been potentially revolutionized by the development of imaging and cerebrospinal fluid (CSF) biomarkers. These biomarkers have influenced the diagnostic evaluation of symptomatic patients with cognitive impairment or dementia, particularly in dementia subspecialty practice. The primary biomarker modalities include magnetic resonance imaging (MRI), positron emission tomography (PET), and CSF.

Related article page 2316

MRI has widely accepted clinical utility for the evaluation of structural brain lesions of a variety of types, including evidence for cerebrovascular disease and atrophy patterns consistent with, but not specific for, neurodegenerative pathologies. PET with ^{18}fluorodeoxyglucose (FDG PET) has strong evidence and a recent practice guideline[1] supports its use as a marker of functional brain abnormalities suggestive of a variety of neurodegenerative pathologies associated with dementia.

Amyloid PET is a Food and Drug Administration–approved biomarker that is sensitive and specific for fibrillar amyloid plaques, a fundamental pathologic feature of AD; an appropriate use guideline specified how amyloid PET could be usefully deployed in subspecialty clinical practice.[2] A recent large study also provided evidence supporting the utility of amyloid PET in dementia subspecialty clinical practice.[3] In addition, several PET tracers that appear to bind to tau-based neurofibrillary tangles (NFTs), the other pathological hallmark of AD, have emerged.[4]

Alternatively, CSF can be analyzed for levels of amyloid-β, as well as tau proteins suggestive of NFTs. A recent practice guideline supports the value of CSF AD biomarkers in the subspecialist evaluation of patients with cognitive impairment or dementia.[5] Thus, these biomarkers are increasingly affecting clinical practice for the evaluation of symptomatic patients with cognitive impairment and are being used extensively in research. While it is clear that these varied tests improve diagnostic accuracy and treatment planning now, their full potential to affect patient outcomes will likely increase with the emergence of more effective therapies.

In parallel, remarkable developments have taken place demonstrating the capacity to measure these biomarkers of key pathological features of AD in cognitively normal individuals. These individuals have been classified as having preclinical AD and the assumption is that a high percentage of those with this pathology will ultimately develop symptomatic disease. Research diagnostic constructs to define preclinical AD were first established in 2011[6] and have been refined using the so-called amyloid, tau, neurodegeneration (AT[N]) system[7] with the recent proposal of a new research framework defining AD using these 3 categories of biomarkers, dichotomously classified as positive or negative, and proposing a separation between the definition of the neuropathological disease and clinical syndromes of cognitive impairment.[8] The AT(N) framework defines AD biologically as requiring the presence of amyloid plaques (ie, A+) and tau neurofibrillary tangles (T+) akin to neuropathological definitions and research is beginning to evaluate this new framework in older adults without dementia. N+ represents neurodegeneration that is typically measured with MRI and FDG PET.

In this issue of *JAMA*, an important new contribution on this topic is reported by some of the originators of this framework.[9] In this article, the authors describe the first study to examine longitudinal clinical outcomes associated with AT(N) classification among 480 individuals without dementia, including mostly cognitively normal adults (92%) and some with mild cognitive impairment. The investigators compared the predictive value of current clinical and genetic measures, including demographic characteristics, *APOE* ε4 status (the strongest genetic risk factor for AD), and cardiovascular and metabolic conditions, with adding the AT(N) classification for prediction of longitudinal decline in memory. The AT(N) framework is still a research construct, and its validation and ultimate utility depend on data supporting its link to clinical outcomes. The authors reported that inclusion of AT(N) biomarkers enhanced prediction of cognitive loss beyond clinical and *APOE* ε4 data alone although this difference was relatively small (R^2 of 0.31 vs 0.26). However, several AT(N) groups were associated with substantially higher rates of annual memory decline (ie, A+T+[N+], A+T+[N−], and A+T−[N+]) that were equivalent to being 20 years older in age. As these groups of patients without dementia who had more extensive AD pathology had faster rates of decline, these findings indicate a potentially useful role of AD biomarkers in forecasting clinical course deterioration among these patients.

Another important contribution of this study is that approximately 50% of the memory change with older age was associated with underlying AD pathology in predementia individuals (estimated based on changes in the prevalence of more AD-enriched AT[N] groups with older age). This supports the concept that a substantial portion of the age-related changes observed in "normal" aging are actually related to the presence of AD-related pathological changes. Yet it remains unclear what factors may account for the other 50% and whether they are linked to distinct other pathologies or reflect nonspecific effects of aging.

The findings of the study by Jack et al[9] may be most immediately relevant for use in clinical trials, allowing patients to be categorized into distinct prognostic groups that are more or less informative regarding therapeutic agent effects. Several current and proposed trials in cognitively normal adults enroll study participants on the basis of a "positive" amyloid PET scan.[10] However, the data in the study by Jack et al[9] suggest that amyloid alone (A+T−[N−]) does not seem to be related to an increased rate of decline (at least over this relatively short follow-up interval) compared with non-AD continuum groups. It was only in the presence of concomitant tau pathology, neurodegeneration, or both that the rate of decline was increased. As such, these latter groups may be more likely to show progression in control groups that could be modified in actively treated groups in prevention studies of only a few years' duration.

However, the analysis by Jack et al[9] also has some potential limitations, many of which were considered by the authors. For instance, the clinical measures included *APOE* ε4, which is highly associated with the presence of cerebral amyloid and may diminish the predictive value of the amyloid PET measure. Also, the clinical variables did not include cognitive measures, which are often linked to the presence of NFTs and neurodegeneration. Their lack of inclusion may overvalue the predictive value of T and (N). Indeed, most (N+) groups tended to have poorer memory at baseline. Further, the groups that displayed the most decline also tended to be associated with lower baseline cognition. Thus, the added value of AT(N) may be smaller with inclusion of cognitive measures, which are generally easier and less expensive to obtain in the clinical context.

Moreover, creating distinct cut-offs (and categories) remains a major hurdle for standardization of AT(N) and dichotomous decisions may be especially challenging along the natural continuum for tau PET and MRI changes. The selection of regions of interest for assessing tau and neurodegeneration also will influence findings because different regions will have variable sensitivity and specificity to different disease stages. In addition, there is no agreement currently on the degree to which these biomarkers, particularly (N), should be controlled for age. Age may have nonspecific effects on morphometric measures of a number of brain regions that may be independent of distinct "pathology." Not controlling for age may reduce specificity to AD-related changes.[11] Notably, age was not fully controlled for in the current analysis and more than 73% of study participants older than 80 years were (N+) compared with 24% of those aged 60 to 69 years who were (N+). Many laboratory diagnostic test values have age-adjusted ranges, which likely would make MRI measures more specific for neurodegeneration as defined by neuropathologists.

An interesting finding in the study by Jack et al[9] was related to the A+T−(N+) category and the fact that patients in this group demonstrated faster cognitive decline than those in the A−T−(N+) group. In both cases, (N) is thought to be driven by non-AD pathology. The underlying etiology in the A−T−(N+) group is unclear. Enriching the framework with measures of other important contributors to age-related cognitive decline, such as vascular, TAR DNA-binding protein 43, and α-synuclein, could increase the diagnostic and prognostic precision of the framework.[12]

In addition, application of AT(N) neuroimaging (an MRI scan and 2 PET scans) is expensive and will not be practical to add to many research projects. The added value of each specific AT(N) measure has not been fully delineated, and requires evaluation in future work, as does whether the findings of the current study will generalize to other biomarkers (CSF, FDG) and more diverse patient populations.

Despite these caveats, the study by Jack et al[9] represents an important contribution not only to advancing the conceptualization of AD, but also for putting this new framework to the test rapidly in a relatively large sample of participants.

ARTICLE INFORMATION

Author Affiliations: Department of Neurology, University of Pennsylvania, Philadelphia (Wolk); Departments of Psychiatry and Neurology, Alpert Medical School, Brown University, Providence, Rhode Island (Salloway); Frontotemporal Disorders Unit & Alzheimer's Disease Research Center, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston (Dickerson).

Corresponding Author: Stephen Salloway, MD, MS, Alpert Medical School, Brown University, Butler Hospital, 345 Blackstone Blvd, Providence, RI 02906 (Stephen_Salloway@brown.edu).

Conflict of Interest Disclosures: Dr Wolk reported receiving grants and personal fees from Avid Radiopharmaceuticals/Eli Lilly and Merck; personal fees from Janssen, GE Healthcare, and Neuronix; and grants from Biogen and Functional Neuromodulation. Dr Salloway reported receiving grants and personal fees from Avid Radiopharmaceuticals/Eli Lilly, Biogen, Roche, Eisai, Genentech, and Novartis. Dr Dickerson reported receiving personal fees from Arkuda, Eli Lilly, Merck, Wave Lifesciences, Novartis, Oxford University Press, Cambridge University Press, and Elsevier; grants and personal fees from Biogen; and grants from the National Institute on Aging, National Institute of Mental Health, and National Institute of Neurological Disorders and Stroke.

REFERENCES

1. Nobili F, Arbizu J, Bouwman F, et al; EANM-EAN Task Force for the Prescription of FDG-PET for Dementing Neurodegenerative Disorders. European Association of Nuclear Medicine and European Academy of Neurology recommendations for the use of brain ^{18}F-fluorodeoxyglucose positron emission tomography in neurodegenerative cognitive impairment and dementia: Delphi consensus. *Eur J Neurol*. 2018;25(10):1201-1217. doi:10.1111/ene.13728

2. Johnson KA, Minoshima S, Bohnen NI, et al; Alzheimer's Association; Society of Nuclear Medicine and Molecular Imaging; Amyloid Imaging Taskforce. Appropriate use criteria for amyloid PET: a report of the Amyloid Imaging Task Force, the Society of Nuclear Medicine and Molecular Imaging, and the Alzheimer's Association. *Alzheimers Dement*. 2013;9(1):e-1-e-16. doi:10.1016/j.jalz.2013.01.002

3. Rabinovici GD, Gatsonis C, Apgar C, et al. Association of amyloid positron emission tomography with subsequent change in clinical management among medicare beneficiaries with mild cognitive impairment or dementia. *JAMA*. 2019;321(13):1286-1294. doi:10.1001/jama.2019.2000

4. Villemagne VL, Doré V, Burnham SC, Masters CL, Rowe CC. Imaging tau and amyloid-β proteinopathies in Alzheimer disease and other conditions. *Nat Rev Neurol*. 2018;14(4):225-236. doi:10.1038/nrneurol.2018.9

5. Shaw LM, Arias J, Blennow K, et al. Appropriate use criteria for lumbar puncture and cerebrospinal fluid testing in the diagnosis of Alzheimer's disease. *Alzheimers Dement*. 2018;14(11):1505-1521. doi:10.1016/j.jalz.2018.07.220

6. Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7(3):280-292. doi:10.1016/j.jalz.2011.03.003

7. Jack CR Jr, Bennett DA, Blennow K, et al. A/T/N: an unbiased descriptive classification scheme for Alzheimer disease biomarkers. *Neurology*. 2016;87(5):539-547. doi:10.1212/WNL.0000000000002923

8. Jack CR Jr, Bennett DA, Blennow K, et al; Contributors. NIA-AA Research Framework: toward a biological definition of Alzheimer's disease. *Alzheimers Dement*. 2018;14(4):535-562. doi:10.1016/j.jalz.2018.02.018

9. Jack CR Jr, Wiste HJ, Therneau TM, et al. Associations of amyloid, tau, and neurodegeneration biomarker profiles with rates of memory decline among individuals without dementia [published June 18, 2019]. *JAMA*. doi:10.1001/jama.2019.7437

10. Touchon J, Rosenbaum J, Aisen P, et al. Editorial: collaborative efforts to prevent Alzheimer's disease. *J Nutr Health Aging*. 2017;21(10):1072-1074. doi:10.1007/s12603-017-0961-9

11. Dickerson BC, Wolk DA; Alzheimer's Disease Neuroimaging Initiative. Biomarker-based prediction of progression in MCI: comparison of AD signature and hippocampal volume with spinal fluid amyloid-β and tau. *Front Aging Neurosci*. 2013;5:55. doi:10.3389/fnagi.2013.00055

12. Wilson RS, Yang J, Yu L, et al. Postmortem neurodegenerative markers and trajectories of decline in cognitive systems. *Neurology*. 2019;92(8):e831-e840. doi:10.1212/WNL.0000000000006949