Editorial

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Blood Tests for Alzheimer's Disease and Related Disorders

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This issue of the Journal of Prevention of Alzheimer's Disease (AD) includes a timely Clinical Trials on AD Task Force Report on promising blood tests for AD and related disorders (1). It highlights the promise of recently developed plasma amyloid-β42/40 (Aβ42/40) measurements for the assessment of neuritic plaque burden (e.g., reference 2), ultrasensitive neurofilament light (NfL) measurements for the assessment of ongoing neuroaxonal injury in a wide range of neurological disorders (3), and their potential roles in evaluation of interventions to treat and prevent the clinical onset of AD. It also considers recently developed plasma total-tau measurements, an indicator of neuronal injury and/or Aβ-mediated tau secretion (4), plasma phospho-tau measurements, a potential indicator of neurofibrillary tangle burden, and the ongoing effort to develop high-dimensional plasma genomic, transcriptomic, metabolomic, lipidomic, and proteomic profiles.

Call to Action

There is an urgent need to develop blood and other fluid biomarkers for AD and related disorders, put them to the test, and support their availability and use in observational studies, therapeutic trials, and clinical practice. Now is the time to establish a comprehensive effort—an AD Fluid Biomarker Initiative—to galvanize the evaluation and deployment of promising blood and cerebrospinal fluid (CSF) tests and use them to help find and support the approval, availability and affordability of interventions to treat and prevent AD as soon as possible.

Why biomarkers for AD and related disorders are so important

Biomarkers of Aβ pathology, tau pathology, and neurodegeneration have had a transformational impact on the fight against AD and related disorders. These and other biomarkers will have increasingly important roles to play in AD research and care. They have been used to detect and track AD starting many years prior to cognitive impairment, leading to the reconceptualization of AD as a progressive sequence of pathophysiological changes that correspond roughly to preclinical and increasingly severe clinical stages. In observational studies, they can be used to inform a person's neuropathological diagnosis and prognosis, evaluate genetic and non-genetic risk factors, clarify the impact of AD pathology on age-related cognitive decline, and inform the design, size and statistical power of treatment and prevention studies. In therapeutic trials, they can be used to select the right research participants, demonstrate target engagement, find optimal drug doses, monitor the safety of Aβ-modifying treatments, and characterize a treatment's effects on progression of Aβ, tau, and neurodegenerative pathology (i.e., provide information about its disease-modifying effects). They can also be used to explore their "predictive" value (i.e., the extent to which baseline measurements can be used to predict a differential response to treatment), characterize their "theragnostic" value (i.e,. the extent to which a treatment's biomarker effects are associated with a clinical response), and provide the evidence needed to support the qualification of biomarkers that appear reasonably likely to be associated with a clinical benefit as "surrogate endpoints" in the accelerated regulatory approval of prevention therapies. When appropriate, available, and informative, an AD biomarker could be used in the clinical setting to inform a person's neuropathological diagnosis, prognosis, and medical and non-medical management.

Brain imaging and CSF biomarkers

To date, the best-established biomarkers of AD include positron emission tomography (PET) measurements of fibrillar Aβ (neuritic plaque) burden, paired helical filament tau (neurofibrillary tangle) burden, and regional cerebral glucose hypometabolism, magnetic resonance imaging (MRI) measurements of regional and whole brain atrophy, and cerebrospinal fluid (CSF) measurements of Aβ pathology, tau pathology and/or neuronal injury (5). Other brain imaging and CSF biomarkers are needed to characterize additional Aβ species, pre-synaptic and post-synaptic neuronal βdegeneration, different neuroinflammatory changes,

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and non-AD (e.g., TDP-43, α-synuclein, and different forms of cerebrovascular disease) pathologies. Despite their importance, PET and MRI studies are expensive, lumbar punctures are invasive, and these procedures are limited in their availability.

Emerging blood tests

If they turn out to have sufficient sensitivity, specificity, precision, and scalability, some of the emerging blood tests could provide inexpensive, widely available, and rapidly repeatable ways to detect and track AD, increase the number of research participants in longitudinal, antemortem-postmortem, treatment and prevention trials with biomarker assessments, and increase the value of these studies in the fight against AD. For instance, a plasma Aβ assay with roughly 90% sensitivity and 50% specificity could be used to screen the population, reduce the number of confirmatory Aβ PET scans, and galvanize the enrollment of Aβ-positive research participants in treatment and prevention trials. If a therapy turns out to treat or prevent AD in persons with a positive Aβ PET scan, the Aβ blood test could be used to screen older adults every 1-2 years, reduce the number of expensive Aβ PET scans or invasive lumbar punctures needed to confirm a positive test, maximize the number of Aβ-positive persons who receive treatment, and help support the treatment's availability around the world. Plasma NfL assays have the potential to monitor the effects of a putative disease-modifying treatment on neuroaxonal injury, repeat these measurements frequently, and provide a potentially early indicator of a treatment's clinical benefit. Unlike brain images, blood samples can be assayed retrospectively, capitalizing on the development of newer biomarkers, and augmenting the value of longitudinal studies and therapeutic trials.

The need for speed

An AD Fluid Biomarker Initiative is needed to provide a shared resource of ample blood samples, CSF samples, DNA and data from thousands of persons with established brain imaging or CSF biomarkers, longitudinal follow-up, and/or subsequent neuropathological assessments, such that promising Aβ blood test and other blood and CSF assays can be put to the test, optimized, and compared as soon as possible. Participants should include those from well characterized longitudinal cohorts, antemortem-postmortem, and real-world clinical settings, including those at different ages, from different ethnic and racial groups, with and without cognitive impairment, and with and without AD and related disorders. Participants should be consented for data and sample sharing, and blood and CSF samples should be acquired, processed and stored, in a standardized way. Data and samples should be stored centrally and made available to researchers using transparent criteria and standardized data sharing and material transfer agreements. Researchers should work together to further develop and test additional CSF and blood tests, support the widespread use of suitable tests, increase the availability of lumbar punctures, and support the clinical availability of an Aβ blood test as soon as possible. They should incorporate suitable tests in clinical trials, and help to find and support the approval, availability and affordability of interventions to treat and prevent AD starting now.

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