Emerging blood-based biomarkers for Alzheimer disease

Emerging blood-based biomarkers for Alzheimer disease are an exciting new development in the dementia field, since they may offer a broadly accessible and relatively inexpensive screening tool. Looking to the future, when disease-modifying or prevention treatments will be available, investigators are focused on how to detect the earliest biological signals of Alzheimer disease, perhaps even years or decades before clinical symptoms appear.

The current standard workup for a patient with dementia symptoms focuses on disorders that may look like dementia or aggravate the early symptoms of Alzheimer disease, or a related dementia (e.g., metabolic disorder, structural abnormality, vitamin deficiency). Currently, patients and their families want to know, Is this Alzheimer disease, or something that can be reversed? Current diagnostic testing can be challenging due to complexity, cost, or level of intervention. A validated blood test that could be widely utilized would be a big step forward for diagnosing and, hopefully, intervening before a patient becomes clinically impaired.

Dementia's Toll

An astonishing 5.8 million Americans age 65 and older have Alzheimer disease or a related dementia, and this number is expected to increase to 13.8 million by 2050.1 The impact on families is both financial and emotional. More than 16 million Americans currently provide unpaid care for family members or friends with dementia. The projected national cost of caring for those with Alzheimer disease and other dementias is currently $305 billion, which is unsustainable. As the aging population increases, so does the population with Alzheimer disease. The burden of caring for the increasing aging population with dementia is exacerbated by a shortage of dementia care specialists and the increasing burden on primary care clinicians to identify and provide care for these patients.1

Early Changes in the Brain Are Hard to Detect

The pathologic hallmarks of Alzheimer disease are the accumulation in the brain of extracellular amyloid beta plaques and intraneuronal inclusions (neurofibrillary tangles) consisting of phosphorylated tau, a microtubule-associated protein. Also present are dystrophic neurites, loss of synapses, neuronal death, and gliosis. These pathologic changes can begin 10 to 20 years before the onset of clinical symptoms.2

Current validated biomarkers of Alzheimer disease pathology include:

• Amyloid beta and tau positron emission tomography (PET)
• The ratio of the concentrations in the cerebrospinal fluid of 2 amyloid beta peptides: the 1–42 peptide and the 1–40 peptide
• The concentrations of total tau and phosphorylated tau (specifically, phosphorylated at amino acid 181) in the cerebrospinal fluid.3,4

The memory specialist is faced with a multitude of nuanced and mixed pathologies underlying a dementia syndrome.3 Biomarkers of Alzheimer disease pathology in combination with cognitive assessment and structural brain imaging can be valuable diagnostic tools in these circumstances. However, cerebrospinal...
fluid analysis and PET are not easily utilized by
the primary care clinician due to access, com-
fort with the testing or interpretation, and
expense. Furthermore, the bedside cognitive
testing currently used by primary care provid-
ers does not easily identify patients with early
cognitive changes.

Therefore, for the primary care clinician,
less-invasive and less-specialized screening
tools, such as a blood test, would be a sig-
nificant development. These screening tools
could help determine who should be referred
for more in-depth testing. Recent develop-
ments in the field are bringing us closer to
blood tests that primary care clinicians can
use as screening tools. This trend is promising,
since it also will help in developing therapies
targeting early-stage Alzheimer disease-specif-
ic pathology in larger and more diverse pop-
ulations. Blood testing could fit into a diag-
nostic algorithm, similar to testing for certain
cancers, that the primary care clinician could
utilize for those at high risk of Alzheimer
disease, such as the elderly and those with a
strong family history.

■ SEARCHING FOR A BLOOD-BASED
BIOMARKER

A major barrier to developing new drugs for
Alzheimer disease is that it is hard to iden-
tify patients who are in the early stage of the
disease, soon after the pathologic changes in
the brain have begun but before cognitive im-
pairment has become apparent, especially in
the primary care setting. Given that an inex-
pensive and sensitive blood-based biomarker
would enhance the ability of the primary care
clinician to screen for possible Alzheimer dis-
ease, many researchers have focused signifi-
cant effort on developing one.

Circulating amyloid beta
In early studies, plasma levels of amyloid beta
lacked a consistent association with Alzheim-
er disease.6 This was most likely due to assay-
related difficulties, since plasma measurements
of this protein may be influenced by matrix ef-
fects whereby other proteins in plasma bind
it. However, later studies using more sensitive
assays indicated that the plasma ratio of the
amyloid beta 1–42 and 1–40 peptides was lower
in amyloid PET-positive individuals, as it is
in the cerebrospinal fluid,7–11 strongly suggest-
ing that a plasma 1–42-to-1–40 ratio may be a
feasible blood-based biomarker of Alzheimer
disease. The only missing piece was a blood-
based measure of tau.

Plasma total tau
Initial studies of blood-based tau suggested that
the plasma total tau concentration is higher in
patients with Alzheimer disease than in cogni-
tively normal controls. Unfortunately, the
difference was not as clear or as well replicat-
ed as in cerebrospinal fluid.6 Subsequent stud-
ies also reported elevated plasma total tau in
Alzheimer disease12,13 and an association with
faster clinical disease progression,12 supporting
the idea that plasma tau is indeed significantly
elevated in Alzheimer disease.

Plasma phosphorylated tau 181, tau 217
Since cerebrospinal fluid phosphorylated tau
181, a key component of neurofibrillary tan-
gles, adds better diagnostic accuracy than tau
alone, researchers developed a new assay for
phosphorylated tau at amino acid 181 in plas-
ma. An association between this new phos-
phorylated tau 181 test and amyloid beta, as
well as tau PET, was even stronger than those
obtained using the plasma total tau test,14–16
strong evidence that plasma-phosphorylated
tau 181 is a feasible blood-based biomarker of
Alzheimer disease. However, since tau is phos-
phorylated at many sites, other phosphorylat-
ed sites may be better circulating biomarkers
of Alzheimer disease. Most recently, intrigu-
ing new findings suggest that the plasma tau
phosphorylated at amino acid 217 differs in
patients with Alzheimer disease compared
with cognitively normal controls and people
with other neurodegenerative disorders.17,18
Plasma phosphorylated tau 217 is an intrigu-
ing finding, since it appears to outperform
plasma phosphorylated tau 181 and imaging
markers in terms of diagnostic accuracy.17,18

■ STUDIES UNDER WAY

While these new findings are encouraging,
they are early results. These blood-based tests
need further testing in large-scale studies over
the long term to refine and verify them, espe-
cially in the general population.

There is as yet no gold standard biomarker
for Alzheimer disease (or for vascular demen-
BEKRIS AND LEVERENZ

REFERENCES

1. Alzheimer’s Association. 2020 Alzheimer’s disease facts and figures. Alzheimers Dement 2020; 16:21. doi:10.1016/j.jalz.2019.12.001

2. Gallardo G, Holtzman DM. Amyloid-β and tau at the crossroads of Alzheimer’s disease. 2020 Alzheimer’s disease facts and figures. 1.

3. Cohen AD, Landau SM, Snitz BE, Klunk WE, Blennow K, Zetterberg H. Fluid and PET biomarkers for amyloid pathology in Alzheimer’s disease. Mol Cell Neurosci 2019; 97:3–17. doi:10.1016/j.mcn.2018.12.001

4. Schöll M, Maass A, Mattsson N, et al. Biomarkers for tau pathology. Mol Cell Neurosci 2019; 97:18-33. doi:10.1016/j.mcn.2018.12.001

5. Boyle PA, Yu L, Leurgans SE, et al. Attributable risk of Alzheimer’s disease and vascular disease. Sci Rep 2016; 6:26801. doi:10.1038/srep26801

6. Verbek IMW, Slot RE, Verfaillie SCJ, et al. Plasma amyloid as prescreener for the earliest Alzheimer pathological changes. Ann Neurol 2018; 84(5):648-658. doi:10.1002/ana.25334

7. Nakamura A, Kaneko N, Villemagne VL, et al. High performance plasma-amyloid biomarkers for Alzheimer’s disease. Nature 2018; 554(7691):249-254. doi:10.1038/nature25456

8. Ovod V, Ramsey KN, Mawuenyega KG, et al. Amyloid-β concentrations and stable isotope labeling kinetics of human plasma specific to central nervous system amyloidosis. Alzheimers Dement 2017; 13(8):841-849. doi:10.1016/j.jalz.2017.06.2266

9. Mielke MM, Hagen CE, Wennberg AMV, et al. Association of plasma total tau level with cognitive decline and risk of mild cognitive impairment or dementia in the Mayo Clinic Study on Aging. JAMA Neurol 2017; 74(9):1073-1080. doi:10.1001/jamaneurol.2017.1359

10. Tatebe H, Kasai T, Ohmichi T, et al. Quantification of plasma phosphorylated tau to use as a biomarker for brain Alzheimer pathology: pilot case-control studies including patients with Alzheimer’s disease and Down syndrome. Mol Neurodegener 2017; 12(1):63. doi:10.1186/s13024-017-0206-8

11. Palmqvist S, Janelidze S, Quirio YT, et al. Discriminative accuracy of plasma phospho-tau181 for Alzheimer disease vs other neurodegenerative disorders. JAMA Neurol 2019; 76(5):698-704. doi:10.1001/jamaneurol.2018.4666

12. Mielke MM, Hagen CE, Xu J, et al. Plasma phospho-tau181 increases with Alzheimer’s disease’s clinical severity and is associated with tau and amyloid-positron emission tomography. Alzheimers Dement 2018; 14(8):898-997. doi:10.1016/j.jalz.2018.02.013

13. Yang C-C, Chiu M-J, Chen T-F, et al. Assay of plasma phosphorylated tau protein (threonine 181) and total tau protein in early-stage Alzheimer’s disease. J Alzheimers Dis 2018; 61(4):1323-1332. doi:10.3233/JAD-170810

14. Barthélemy NR, Horie K, Sato C, Bateman RJ. Blood plasma phosphorylated-tau isoforms track CNS change in Alzheimer’s disease. J Exp Med 2020; 217(11):e20200861. doi:10.1084/jem.20200861

15. Carrillo MC, Blennow K, Soares H, et al. Global standardization measurement of cerebral spinal fluid for Alzheimer’s disease: an update from the Alzheimer’s Association Global Biomarkers Consortium. Alzheimers Dement 2013; 9(2):137-140. doi:10.1016/j.jalz.2012.11.003

Address: Lynn M. Bekris, PhD, Genomic Medicine Institute, R4, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; bekris@ccf.org

Cleveland Clinic Journal of Medicine Volume 87 • Number 9 • September 2020

539

Downloaded from www.ccjm.org on July 11, 2022. For personal use only. All other uses require permission.