A blood test for Alzheimer’s would be a great advance for individuals with — and at risk for — the disease, families, doctors and researchers.

At the Alzheimer’s Association International Conference® (AAIC®) 2020, scientists reported results of multiple studies on advances in blood “tests” for abnormal versions of the tau protein, one of which may be able to detect changes in the brain 20 years before dementia symptoms occur. In particular, the reports focus on a specific form of tau known as p-tau217, which seems to be the most specific to Alzheimer’s and the earliest to show measurable changes.

Changes in brain proteins amyloid and tau, and their formation into clumps known as plaques and tangles, respectively, are defining physical features of Alzheimer’s disease in the brain. Buildup of tau tangles is thought to correlate closely with cognitive decline. In these newly reported results, blood/plasma levels of p-tau 217, one of the forms of tau found in tangles, also seem to correlate closely with buildup of amyloid.

Currently, the brain changes that occur before Alzheimer’s dementia symptoms appear can only be reliably assessed by positron-emission tomography (PET) scans, and from measuring amyloid and tau proteins in spinal fluid (CSF). These methods are expensive and invasive. And, too often, they are unavailable because they are not covered by insurance or difficult to access, or both.

“There is an urgent need for simple, inexpensive, non-invasive and easily available diagnostic tools for Alzheimer’s. New testing technologies could also support drug development in many ways. For example, by helping identify the right people for clinical trials, and by tracking the impact of therapies being tested,” said Maria C. Carrillo, Ph.D., Alzheimer’s Association chief science officer. “The possibility of early detection and being able to intervene with a treatment before significant damage to the brain from Alzheimer's disease would be game changing for individuals, families and our healthcare system.”

A blood test, for example, will enable interpretation and understanding of Alzheimer’s progression in much larger, more diverse and more robust populations.

“While these new reports are encouraging, these are early results, and we do not yet know how long it will be until these tests are available for clinical use. They need to be tested in long-term, large-scale studies, such as Alzheimer’s clinical trials,” Carrillo added. “In addition, we need to continue research to refine and verify the tests that are the current state-of-the-art — including cerebrospinal fluid and PET imaging biomarkers.”
Blood P-tau217 Detects Alzheimer’s Disease (i.e., Both Plaques and Tangles) with High Accuracy

As reported at AAIC 2020, an international team of researchers have identified a highly accurate, blood-based biomarker for the detection of Alzheimer’s disease by measuring levels of p-tau217 in blood, and validated the finding in multiple, diverse populations. The scientists found that, “the diagnostic precision of blood p-tau217 was as high as established diagnostic methods, including positron emission tomography (PET) imaging and cerebrospinal fluid biomarkers, which are invasive, costly and less available.”

The research team was led by Oskar Hansson, M.D., Ph.D., from Lund University, Sweden in coordination with Sebastian Palmqvist, M.D., Ph.D., and Shorena Janelidze, Ph.D. from Lund, Eric Reiman, M.D., from Banner Alzheimer’s Institute, USA, Jeffrey Dage, Ph.D., from Eli Lilly, USA, and other research colleagues. The Lund University researchers presented the results at AAIC, and they were also published online.

They studied three different cohorts comprising more than 1,400 cases, including a large clinic-based study from Sweden (the BioFINDER-2 study), a cohort with neuropathological confirmation of Alzheimer’s (the Arizona Study of Aging and Neurodegenerative Disorders), and a large kindred with genetically-caused Alzheimer’s (Colombian autosomal-dominant Alzheimer’s registry). They analyzed other current experimental biomarkers (p-tau217, p-tau181, Aβ42/40 and neurofilament light chain) in both blood and cerebrospinal fluid, as well as performed PET imaging for tau and amyloid pathology.

The main finding of the study was that blood p-tau217 could distinguish Alzheimer’s from other neurodegenerative disorders with diagnostic accuracy between 89 and 98 percent. In this study, the p-tau217 assessment was more accurate for Alzheimer’s than blood-based tests for p-tau181, neurofilament light or amyloid beta 42/40 ratio, as well as magnetic resonance imaging (MRI). In fact, according to the researchers, performance was similar to significantly more costly methods, such as PET imaging and cerebrospinal fluid biomarkers.

The researchers also found that p-tau217 analyzed in blood collected during life could detect tau brain changes measured in brain tissue analyzed after death. These tau brain changes are thought to be related to amyloid plaque accumulation. P-tau217 distinguished persons who had plaques and tangles from those without Alzheimer’s pathology with 89% accuracy, those with plaques and more extensive tangles with 98% accuracy, and the outcome of tau PET imaging with 93% accuracy.

The p-tau217 levels were increased about seven-fold in Alzheimer’s, and, in individuals with a gene causing Alzheimer’s, the levels started to increase already 20 years before onset of cognitive impairment. “This test, once verified and confirmed, opens the possibility of early diagnosis of Alzheimer’s before the dementia stage, which is very important for clinical trials evaluating novel therapies that might stop or slow down the disease process,” Hansson said.

Blood Amyloid and P-tau are Precise Markers of Brain Amyloidosis, Tauopathy

To advance research on a blood test for Alzheimer’s disease, Suzanne Schindler, M.D., Ph.D., of Washington University School of Medicine in St. Louis and colleagues evaluated the performance of a variety of amyloid and tau measures in blood.

Using mass spectrometry, the scientists mapped the blood plasma tau protein and compared the results to CSF and PET imaging measures. Compared to the better-known tau form p-tau181, they found that p-tau217 was more closely linked to build up of amyloid plaques in the brain as measured by a PET scan.

Additionally, their findings suggest that measuring levels of several different forms of p-tau in blood over
time may enable clinicians and researchers to track the stages of Alzheimer’s progression in people living with the disease.

According to the researchers, a blood test for Alzheimer’s disease that incorporates both amyloid and tau measures may allow earlier and more accurate dementia diagnoses not only in research participants but also in clinic patients.

The scientists launched the Study to Evaluate Amyloid in Blood and Imaging Related to Dementia (SEABIRD) to develop and validate Alzheimer’s blood biomarkers in a cohort that is more diverse and representative of the greater St. Louis region. SEABIRD will enroll more than 1,100 individuals including diversity in race, socioeconomic status, medical history and cognitive status.

**Plasma P-tau217 is Comparable to P-tau181 for Distinguishing Between Alzheimer’s and Frontotemporal Lobar Degeneration**

Recent studies have shown that p-tau181 is more than three times as high in people with Alzheimer’s compared to healthy elderly people or people with a neurodegenerative disease known as frontotemporal lobar degeneration (FTLD). At AAIC 2020, Elisabeth Thijssen, M.Sc., and Adam L. Boxer, M.D., Ph.D., of the UCSF Memory and Aging Center and colleagues reported a comparison of p-tau181 to a related form of tau called p-tau217 to determine which form can best identify people with Alzheimer’s.

The retrospective study included 617 participants: 119 healthy controls, 74 Alzheimer’s cases (biomarker-confirmed) and 294 FTLD. In this study group, plasma p-tau181 was increased three-fold in people with Alzheimer’s compared to controls and FTLD. Increase in plasma p-tau217 was even higher; five-fold in Alzheimer’s compared to healthy controls and four-fold relative to FTLD. The plasma comparison results mirrored the findings of tau PET imaging in the brain. P-tau181 had a 91% accuracy and p-tau217 had 96% accuracy in predicting whether a person had a tau positive brain scan.

According to the researchers, the study shows that both p-tau217 and p-tau181 measured in blood are elevated in Alzheimer’s, and that measurements closely correspond to “gold standard” PET scan results. These blood tests are likely to be useful for diagnosing Alzheimer’s and as monitoring tools in clinical trials to measure treatment effects of new Alzheimer’s therapies.

**About the Alzheimer’s Association International Conference (AAIC)**
The Alzheimer’s Association International Conference (AAIC) is the world’s largest gathering of researchers from around the world focused on Alzheimer’s and other dementias. As a part of the Alzheimer’s Association’s research program, AAIC serves as a catalyst for generating new knowledge about dementia and fostering a vital, collegial research community.

- AAIC 2020 hashtag: #AAIC20

**About the Alzheimer’s Association**
The Alzheimer’s Association is a worldwide voluntary health organization dedicated to Alzheimer’s care, support and research. Our mission is to lead the way to end Alzheimer’s and all other dementia — by accelerating global research, driving risk reduction and early detection, and maximizing quality care and support. Visit [alz.org](http://alz.org) or call 800.272.3900.

###
Oskar Hansson, PhD, et al. Phospho-tau217 and phospho-tau181 in plasma and CSF as biomarkers for Alzheimer’s disease. (Funder(s): Swedish Research Council, the Knut and Alice Wallenberg Foundation, and the Swedish Alzheimer Foundation)

Shorena Janelidze, PhD, et al. Plasma phospho-tau217 is a potential early diagnostic and prognostic biomarker of Alzheimer’s disease. (Funder(s): Swedish Research Council, the Knut and Alice Wallenberg Foundation, and the Swedish Alzheimer Foundation)

Suzanne Schindler, MD, PhD, et al. Mass spectrometry measures of plasma Aβ, tau and p-tau isoforms relationship to amyloid PET, tau PET, and clinical stage of Alzheimer’s disease. (Funder(s): U.S. National Institute on Aging)

Elisabeth Thijssen, MSc, et al. Comparative diagnostic performance of plasma P-tau217 and P-tau181 in Alzheimer’s Disease and Frontotemporal Lobar Degeneration and correlations with [18F]Flortaucipir-PET uptake. (Funder(s): U.S. National Institute on Aging, National Center for Advancing Translational Sciences, Tau Research Consortium)

*** AAIC 2020 news releases may contain updated data that does not match what is reported in the following abstracts.
Phospho-tau217 and phospho-tau181 in plasma and CSF as biomarkers for Alzheimer’s disease
Proposal ID: 37520, F4-01-03

Tuesday, July 28, 2020, 12:10 pm CT
VFairs, The Hague

Background: Cerebrospinal fluid (CSF) p-tau181 (tau phosphorylated at threonine 181) is an established biomarker of Alzheimer’s disease (AD) reflecting abnormal tau metabolism in the brain. We have recently shown that also plasma p-tau181 is a promising biomarker for AD (Janelidze et al, *Nature Medicine*, 2020). We now evaluate whether CSF p-tau217 or plasma p-tau217 are even better biomarkers.

Methods: We compared CSF p-tau217 to CSF p-tau181 in the Swedish BioFINDER-1 cohort (n=194). We next evaluated plasma p-tau217 and plasma p-tau181 in three cohorts with 1,438 participants: an Arizona-based neuropathology cohort, including 34 AD and 47 non-AD participants; the Swedish BioFINDER-2 cohort, including cognitively unimpaired (n=312) participants, and clinically diagnosed patients with mild cognitive impairment (MCI, n=188), AD dementia (n=126), and other non-AD neurodegenerative diseases (n=109); a Colombian autosomal-dominant AD kindred, including 365 PSEN1E280A-carriers and 257 non-mutation carriers.

Results: CSF p-tau217 had stronger correlations with the tau-PET tracer, and more accurately identified individuals with abnormal tau-PET scans (AUC=0.93) than CSF P-tau181. CSF P-tau217 correlated better than p-tau181 with CSF and PET measures of neocortical amyloid-β burden and more accurately distinguished AD dementia from non-AD neurodegenerative disorders. Antemortem plasma P-tau217 differentiated individuals with intermediate-to-high likelihood of AD according to neuropathology from those without AD (AUC=0.89) and performed significantly better than plasma P-tau181. Plasma P-tau217 also differentiated clinical AD dementia from non-AD neurodegenerative diseases (AUC=0.96) significantly better than plasma P-tau181, plasma neurofilament light, and established MRI measures, and similar to CSF P-tau217, CSF P-tau181, CSF Aβ42/40, and tau-PET. Increased plasma P-tau217 was observed already in the pre-symptomatic stages of AD. In PSEN1 mutation carriers the increase started at age 25, about 20 years prior to estimated onset of MCI. Plasma P-tau217 correlated with cerebral tau tangle densities in subjects with neuritic plaques (r=0.64). It predicted abnormal tau-PET scans (AUC=0.95) significantly better than plasma P-tau181, plasma neurofilament light, CSF P-tau181 and CSF Aβ42/Aβ40, and similar to CSF P-tau217.

Conclusions: Plasma and CSF P-tau217 reflect brain tau burden, increases early in AD, and differentiates AD from other neurodegenerative diseases.

Presenting author
Oskar Hansson, PhD Email: oskar.hansson@med.lu.se
Clinical Memory Research Unit, Lund University, Malmö 221 84, Sweden
Plasma phospho-tau217 is a potential early diagnostic and prognostic biomarker of Alzheimer’s disease
Proposal ID: 42489

Tuesday, July 28, 2020, 12:00 am CT
Posters: Biomarkers

**Background:** There is an urgent need for inexpensive and minimally invasive blood biomarkers of Alzheimer’s disease (AD) that could be used to detect early disease changes.

**Method:** We measured plasma levels of tau phosphorylated at threonine 217 (P-tau217) in the prospective Swedish BioFINDER (BF) I and II studies (n=1057). BF-II included cognitively unimpaired individuals (CU, n=275) and patients with mild cognitive impairment (MCI, n=161), AD dementia (n=114) and non-AD neurodegenerative diseases (n=91) who underwent tau-PET imaging using [18F]RO948. A subcohort of 157 participants had two or three tau-PET scans on average 1.0 years apart (range 0.1-1.6 years). In BF-I, 264 CU and 152 MCI were followed longitudinally with clinical examinations to determine conversion to AD dementia (mean follow-up 4.9 years, range 1.0-8.6 years).

**Result:** Plasma P-tau217 levels were increased in CU individuals with abnormal amyloid-β (Aβ)-PET but still normal tau-PET in the earliest Braak I-II (entorhinal) ROI (Aβ-PET\textsuperscript{pos}/tau-PET\textsuperscript{neg} group vs Aβ-PET\textsuperscript{neg}/tau-PET\textsuperscript{neg} group, p<0.001). Furthermore, when testing the relation to global Aβ load in non-linear spline models (Figure 1), we found that plasma P-tau217 started to increase at Aβ-PET SUVR of 0.39, which preceded the increase in tau-PET measures (Aβ-PET SUVR 0.42-0.62). In line with these data, the majority of cases that were discordant for plasma P-tau217 and tau-PET in Braak I-II were positive for P-tau217 and negative for tau-PET (P-tau217\textsuperscript{pos}/tau-PET\textsuperscript{neg}, n=68 [72%] and P-tau217\textsuperscript{neg}/tau-PET\textsuperscript{pos}, n=27 [28%]). Among participants with normal baseline tau-PET, the rates of longitudinal increase in tau-PET in the Braak I-II ROI were higher in cases with abnormal plasma the P-tau217 at baseline (p=0.017). Finally, in non-demented individuals, abnormal levels of P-tau217 were associated with increased risk of future AD dementia (hazard ratio 5.4; 95% confidence interval 3.5-8.4; p<0.001).

**Conclusion:** Plasma P-tau217 levels increase in early stages of AD when insoluble tau aggregates are not yet detectable by tau-PET and predict both subsequent increase in tau-PET as well as conversion to AD dementia. Plasma p-tau217 holds promise as a marker for early AD-pathology.

**Presenting Author**
Shorena Janelidze, PhD  
Email: Shorena.janelidze@med.lu.se  
Clinical Memory Research Unit, Lund University, Malmö 221 84, Sweden

*Figure1.jpg (733.1KB)*
Mass spectrometry measures of plasma Aβ, tau and p-tau isoforms relationship to amyloid PET, tau PET, and clinical stage of Alzheimer’s disease

Proposal ID: 37518, F4-01-01

Tuesday, July 28, 2020, 11:30 am CT
VFairs, The Hague

**Background:** Recent advances in understanding the links between amyloid-beta (Aβ) and specific tau isoforms in brain, cerebrospinal fluid (CSF), and blood indicate that a cascade of events of Alzheimer’s disease (AD) pathophysiology begin with detection of altered CSF and blood Aβ 42/40 ratio, followed by increases in amyloid plaques by Positron Emission Tomography (PET) scan, associated with increased phosphorylation of specific CSF tau isoforms (e.g. p-tau217 and p-tau181), before increases in p-tau205, hypometabolism, and atrophy. Finally, CSF total tau increases before tau aggregation by tau PET and onset of clinical symptoms. The longitudinal tau and Aβ changes which occur in brain and CSF are now being understood in blood, enabling interpretation and understanding of AD progression in much larger and more robust populations.

**Method:** We compared plasma Aβ 42/40 ratios measured by mass spectrometry to measures of amyloid, tau, and clinical and cognitive status in ADNI, AIBL, Biofinder and the Knight ADRC. In order to improve racial, ethnic, educational, socioeconomic, and comorbid disease diversity, we launched the Study to Evaluate Amyloid in Blood and Imaging Related to Dementia (SEABIRD), a community- and clinic-based study (goal n=1120) to mirror the demographics of the Saint Louis metropolitan area. We mapped the entire blood plasma tau protein with 15 specific regions and analyzed several plasma p-tau isoforms (e.g. p-tau217 and p-tau181) by mass spectrometry and compared with CSF and PET results across two sporadic AD studies.

**Result:** SEABIRD participants had an initial blood collection and 25% underwent confirmatory amyloid PET. Consistent with ADNI, AIBL, Biofinder and ADRC, we found plasma Aβ 42/40 ratios had high concordance with amyloid PET. In blood plasma tau, we found that some, but not all, plasma p-tau isoforms had a strong concordance with CSF and PET measures and that p-tau217 was more concordant for amyloid status compared to p-tau181. Further, plasma Aβ 42/40 and p-tau measures identify the stage of disease as measured by PET and CSF measures, figure 1.

**Conclusion:** These findings indicate that blood plasma Aβ and p-tau measures are highly precise biomarkers of brain amyloidosis, tauopathy, and can identify stages of clinical and preclinical AD.

**Presenting author**
Suzanne Schindler, MD, PhD     Email: schindler.s.e@wustl.edu
Washington University in St. Louis School of Medicine, St. Louis MO 63110

**Fig 1_Rv.PNG (129.3KB)**
Comparative diagnostic performance of plasma P-tau217 and P-tau181 in Alzheimer’s Disease and Frontotemporal Lobar Degeneration and correlations with [18F]Flortaucipir-PET uptake

Proposal ID: 45755

Tuesday, July 28, 2020, 12:00 am CT
Posters: Biomarkers

**Background:** Plasma P-tau181 has previously been shown to be associated with tau pathology in Alzheimer’s disease (AD). P-tau217 is a novel blood-based biomarker. We assessed the diagnostic value of plasma P-tau181 and P-tau217 in the same cohort of patients across the AD and frontotemporal lobar degeneration (FTLD) spectrum.

**Method:** This retrospective study of 617 participants included 119 healthy controls, 74 cases in the clinical AD spectrum (57 amnestic, 15 lvPPA, 2 PCA; all biomarker-confirmed) and 294 in the FTLD spectrum. The cohort included 15 AD and 67 FTLD autopsy-confirmed cases and 66 Microtubule-Associated Protein Tau (MAPT) mutation carriers. P-tau concentrations were measured using custom electrochemiluminiscence-based assays at Lilly. P-tau217 was available in 513 cases, P-tau181 in 614 cases, and both in 509. Amyloid-PET was available in 352 cases and [18F]Flortaucipir (FTP)-PET in 227 cases. The differentiating power of P-tau181 and P-tau217 was assessed across clinical and autopsy-confirmed phenotypes, amyloid- and FTP-PET status, and type of tau pathology in MAPT mutation carriers.

**Result:** Plasma P-tau217 concentrations were increased 5.2-fold in clinical AD (n=74) relative to controls (AUC=97%, p<0.001) and 3.8 fold relative to clinical FTLD (AUC=93%, p<0.001). P-tau217 was increased 4.9 fold in autopsy-confirmed AD compared to autopsy-confirmed FTLD (AUC=92%, p<0.001). Plasma P-tau181 was increased 2.6 fold in clinical AD compared to controls (AUC=93%, p<0.001) and 2.4 fold relative to clinical FTLD (AUC=89%, p<0.001). P-tau181 was increased 2.5 fold in autopsy-confirmed AD compared to autopsy-confirmed FTLD (AUC=87%, p<0.001). There was no change in P-tau217 concentrations in MAPT mutation carriers with mixed 3R/4R tau pathology compared to 4R tau pathology, whereas P-tau181 was 1.4 fold increased (p<0.01). FTP-PET SUVR was associated with P-tau217 (ρ=0.78, p<0.001) and P-tau181 (ρ=0.64, p<0.001). P-tau217 could identify amyloid-PET positive cases (n=317, AUC= 86%, p<0.001), and FTP-PET positive cases (AUC= 96%, p<0.001, n=213) across diagnoses, with similar accuracy to P-tau181 (amyloid-PET AUC=81%, n=351, FTP-PET AUC=90%, p<0.001, n=227).

**Conclusion:** Plasma P-tau217 is comparable to P-tau181 for differential diagnosis of AD and potentially superior for identifying FTP-PET positivity. Additional investigations are necessary to explain potential differences in assay performance in MAPT mutation carriers that produce mixed 3R/4R tau, whose pathology is similar to AD.

**Presenting Author**
Elisabeth Thijssen, MSc  
Email: e.thijssen@amsterdamumc.nl  
UCSF Memory and Aging Center