Quanterix®

Fact Sheet

Simoa® p-Tau 181

What is p-Tau 181?

Tau is a microtubule-stabilizing protein primarily expressed in central nervous system (CNS) neurons, but also at low levels in astrocytes and oligodendrocytes. Tau consists of six isoforms in the human brain with molecular weights ranging from 48-67 kDa. Under physiological conditions, tau is primarily localized within neurons. However, elevated tau in cerebrospinal fluid (CSF) is a hallmark of neurodegenerative diseases and severe brain injuries, indicating its extracellular release during neuronal damage. In Alzheimer's disease (AD) and related conditions, tau becomes abnormally phosphorylated, forming filamentous bundles. Among its phosphorylation sites, aberrant phosphorylation of tau at threonine 181 (p-Tau 181) leads to the formation of neurofibrillary tangles, a hallmark pathological feature of AD. Elevated levels of p-Tau 181 in CSF and blood have been consistently associated with cognitive decline and neurodegeneration in AD patients, making p-Tau 181 a valuable diagnostic and prognostic marker.

How to Measure p-Tau 181?

The Simoa® p-Tau 181 assay is an ultra-sensitive digital immunoassay for the quantitative determination of p-Tau 181 in human serum, EDTA plasma and CSF. Quanterix also offers Simoa® p-Tau 181 testing in human EDTA plasma and CSF as a Laboratory Developed Test (LucentAD) that has been validated under CLIA. This test is not currently cleared by the U.S. FDA as an in vitro diagnostic.

What is the Simoa® Difference?

Simoa® is a powerful digital immunoassay technology that is up to 1000 times more sensitive than standard sandwich-based immunoassay techniques. Traditional ELISA measurements are limited to pg/ml levels of detection. Quanterix Simoa® can achieve sensitivity as low as femtogram (fg/ml) levels, delivering the gold standard for early, ultra-sensitive detection and quantification of proteins far below the typical lower limit of quantification (LLOQ).

Simoa® is based upon the isolation of individual immunocomplexes on paramagnetic beads using standard ELISA reagents. The main difference between Simoa® and conventional immunoassays lies in the ability to trap single molecules in femtoliter-sized wells, allowing for a "digital" readout of each individual bead to determine if it is bound to the target analyte or not.

Simoa® p-Tau 181 testing is offered by Quanterix as a lab developed test (Lucent AD) per CLIA and CLSI guidelines. Quanterix's state-of-the-art facility includes a CLIA-licensed lab and supports over 400 customers globally.

Neurological disorders continue to be among the most challenging to diagnose early and treat. Unlike 'visible' illnesses, neuronal injury and neurodegeneration can be overlooked or mistaken for other conditions. The subtlety of symptoms and the subjective nature of today's assessments also make it difficult to identify these diseases early. Currently, no definitive tests exist for the early detection of neurodegenerative diseases such as AD. Clinicians can only conclusively diagnose them once symptoms start to present. As a result, many patients may wait years for a diagnosis or a clear treatment pathway.

p-Tau 181 has emerged in recent years as valuable biomarker of AD pathology and neuronal injury, establishing itself as a promising tool for evaluating AD pathology. Its specificity to AD pathology distinguishes it from other biomarkers and underscores its importance in clinical research and practice. Furthermore, advancements in assay technologies, such as Simoa® technology have facilitated the accurate and ultra-sensitive quantification of p-Tau 181 levels in biofluids, enhancing its utility in early detection and differential diagnosis of AD. Thousands of studies have validated the use of Simoa® immunoassays to detect and measure biomarkers that hold promise as tools for early detection and prognosis for a range of neurodegenerative conditions.

p-Tau 181 in Action

Differential diagnosis of mild cognitive impairment of Alzheimer's disease by Simoa® p-Tau 181 measurements with matching plasma and CSF

Alzheimer's disease has a prolonged preclinical phase. Late-stage AD can be distinguished from normal cognition using clinical evaluation, PET imaging, and biofluid biomarkers. However, distinguishing mild cognitive impairment (MCI) subtypes from normal cognition remains challenging. This study assessed p-Tau 181's ability to diagnose MCI and differentiate amnestic (aMCI) from non-amnestic (naMCI) MCI. While p-tau181 robustly differentiate MCI or aMCU from cognitively normal cohorts, it struggled to distinguish aMCI from naMCI. Adding Aβ or total tau levels improved aMCI diagnosis.

Wu L, Arvai S, Wang SJ, Liu AJ, Xu B. Differential diagnosis of mild cognitive impairment of Alzheimer's disease by Simoa p-tau181 measurements with matching plasma and CSF. *Front Mol Neurosci.* 2024;16:1288930. Published 2024 Jan 8. doi:10.3389/fnmol.2023.1288930

Potential Utility of Plasma Biomarker Panels in Differential Diagnosis of Alzheimer's Disease

Blood tests are in need for Alzheimer's diagnosis, offering less invasive and cheaper options than cerebrospinal fluid or neuroimaging. Plasma samples from AD, healthy, and non-AD subjects were examined for Aβ42, t-Tau, p-Tau 181, and NfL using Simoa® immunoassays. The results of this study show this panel of plasma biomarkers, alongside clinical assessments may aid in distinguishing AD and other dementias from healthy individuals.

Krishna G, Thangaraju Sivakumar P, Dahale AB, Subramanian S. Potential Utility of Plasma Biomarker Panels in Differential Diagnosis of Alzheimer's Disease. *J Alzheimers Dis Rep.* 2024;8(1):1-7. Published 2024 Jan 9. doi:10.3233/ADR-230156

Association of Plasma Phosphorylated Tau with the Response to Neflamapimod Treatment in Patients with Dementia with Lewy Bodies

In patients with dementia with Lewy bodies (DLB), Alzheimer's disease copathology often leads to faster cognitive decline and more severe brain atrophy. This study aimed to understand how a biomarker of AD copathology, plasma p-Tau 181, relates to treatment outcomes with neflamapimod, a drug targeting cholinergic degeneration in DLB. In a phase 2a clinical trial, participants were categorized based on their plasma p-Tau181 levels. Results showed that those with lower p-Tau 181 levels experienced greater improvements with neflamapimod treatment, suggesting that screening for p-Tau 181 could help identify DLB patients who may benefit most from such therapies.

Alam JJ, Maruff P, Doctrow SR, et al. Association of Plasma Phosphorylated Tau With the Response to Neflamapimod Treatment in Patients With Dementia With Lewy Bodies. *Neurology.* 2023;101(17):e1708-e1717. doi:10.1212/WNL.0000000000207755

Trajectories of CSF and plasma biomarkers across Alzheimer's disease continuum: disease staging by NF-L, p-Tau 181, and GFAP

The study explored the potential of transitioning Alzheimer's disease molecular phenotyping from cerebrospinal fluid to plasma samples across various stages of AD. Core biomarkers like Aβ42/40, p-Tau 181, and t-Tau showed correlation between CSF and plasma. GFAP, NF-L, and p-Tau 181 were identified as significant markers for disease progression in both CSF and plasma. These results suggest the potential for using a standardized panel of plasma markers to aid in early AD diagnosis and disease monitoring.

Wojdała AL, Bellomo G, Gaetani L, et al. Trajectories of CSF and plasma biomarkers across Alzheimer's disease continuum: disease staging by NF-L, p-tau181, and GFAP. *Neurobiol Dis.* 2023;189:106356. doi:10.1016/j.nbd.2023.106356

Plasma p-Tau 181 as a biomarker of mild traumatic brain injury: findings from THINC and NCAA-DoD CARE Consortium prospective cohorts

This study investigated plasma p-Tau 181 protein levels in mild traumatic brain injury (mTBI) patients and concussed athletes. Two cohorts were studied: one with mTBI patients (n = 288) and uninjured controls (n = 30), and another with concussed athletes (n = 112) and uninjured athletes (n = 21). Plasma p-Tau 181 levels were significantly elevated within 48 hours of injury, particularly within 18 hours. Higher levels correlated with positive neuroimaging findings. These results suggest plasma p-Tau 181 as a potential early diagnostic biomarker for mTBI/concussions.

Devoto C, Vorn R, Mithani S, et al. Plasma phosphorylated tau181 as a biomarker of mild traumatic brain injury: findings from THINC and NCAA-DoD CARE Consortium prospective cohorts. *Front Neurol.* 2023;14:1202967. Published 2023 Aug 17. doi:10.3389/fneur.2023.1202967

Plasma neurofilament light-chain and phosphorylated tau as biomarkers of disease severity in Huntington's disease: Korean cohort data

This study on Korean Huntington's disease (HD) patients examined plasma markers—neurofilament light chain, p-Tau 181, and total tau—in relation to disease severity. 67 genetically confirmed HD patients from 13 hospitals were evaluated using various scales. Plasma NfL levels were elevated in both premanifest and manifest HD patients, with a notable increase from premanifest to manifest stages. Plasma p-Tau 181 levels were elevated, particularly in later stages, correlating with disease severity. These findings suggest NfL as an early HD biomarker and p-Tau 181 as a marker of HD severity.

Hwang YS, Oh E, Kim M, et al. Plasma neurofilament light-chain and phosphorylated tau as biomarkers of disease severity in Huntington's disease: Korean cohort data. *J Neurol Sci.* 2023;452:120744. doi:10.1016/j.jns.2023.120744

p-Tau 181 in the News

The Role of p-Tau 181 in LEQEMBI®'s Development and Approval

During the development of LEQEMBI®, the inclusion of p-Tau 181 measurements played an important role. LEQEMBI® is a humanized IgG1 monoclonal antibody that specifically targets β-amyloid plaques and is the first disease modifying therapy fully approved by the FDA for AD patients. The results of the LEQEMBI® clinical trials demonstrated a slowing of AD progression, improved quality of life and decreased care partner burden. Additionally, LEQEMBI®'s impact on AD associated biomarkers, including p-Tau 181, was assessed to help elucidate a biological basis for the treatment effects consistent with slowing of disease progression.

By measuring p-Tau 181 levels in CSF and plasma, researchers were able gain insights into LEQEMBI®'s impact on tau pathology, treatment effect and its potential to slow down the progression. Clinical trial data demonstrated that LEQEMBI® treatment resulted in the reduction of CSF and plasma p-Tau 181 levels in a dose- and time-dependent manner. Taken together with the improvement observed with other AD associated biomarkers (including Aβ42-40 and GFAP), this incorporation of p-Tau 181 measurements not only provided evidence of drug efficacy but also contributed to understanding how LEQEMBI® modifies underlying disease pathology, therefore enhancing the understanding of treatment response.

For more information visit https://www.quanterix.com/simoa-assay-kits/p-tau181-v2-new/