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WHITEPAPER

The Evolving Role of Tau in Neurodegeneration:
A comprehensive look at biomarkers and clinical applications

The microtubule-associated protein Tau has emerged as a pivotal biomarker for neurodegenerative disorders, particularly for developing biomarkers for diagnosis, prognosis, and treatment options for Alzheimer's disease (AD). Tau is predominantly expressed in neurons and functions to stabilize microtubules, the principal cytoskeletal component, to maintain neuronal structure. Hyperphosphorylated Tau is linked to impaired microtubule binding, neuronal degeneration, Tau aggregation, and the formation of neurofibrillary tangles (NFTs) in neurons – one of the two hallmarks of AD, along with extracellular amyloid plaques (Figure 1).[1, 2, 3]

Given the critical physiological and pathological roles of Tau, biomarkers centered on Tau, evaluated in the brain, cerebrospinal fluid (CSF), and blood, have been highly sought after for their potential in improving the understanding, identification, and tracking of AD pathology. While Tau-positron emission tomography (Tau-PET) brain imaging remains the gold standard for detecting and measuring the degree of NFTs, the expensive and specialized nature of PET makes it infeasible for large-scale implementation. Cerebrospinal fluid (CSF) has been a major fluid sampling approach for Tau biomarkers but requires an invasive procedure. These factors limit the practical use of imaging and CSF biomarkers in detecting the disease at prodromal or preclinical stages when treatment and care are most effective.

In recent years, fueled by the advent of highly sensitive protein detection technologies such as the Simoa® digital immunoassay, research into blood Tau biomarkers has accelerated at an extraordinary pace and continues to break new ground in precision AD diagnosis. These Tau

biomarkers include total Tau (t-Tau), multiple phosphorylated Tau (p-Tau) variants like p-Tau 181, p-Tau 217, and emerging markers such as brain-derived Tau (BD-Tau), and microtubule-binding region (MTBR) Tau containing residue 243 (MTBR-Tau243). This whitepaper summarizes the status of Tau biomarkers, explores methods for measuring different forms of Tau, and examines their applications in research and clinical studies.

An Expansive Menu of Tau Biomarkers

Tau is a multifaceted protein with diverse isoforms, a large array of posttranslational modifications (PTMs), and complex physiological and pathological roles.[1] In the adult human brain, Tau exists in six main isoforms generated by alternative splicing around the N-terminal region and the MTBR. The longest form of Tau in the human brain, also known as 2N4R Tau, is 441-aa long as shown in Figure 2. Tau is subjected to phosphorylation at many serine and threonine sites in both physiological and pathological conditions, with key phospho-epitopes highlighted in red.[4]

It is believed that phosphorylation of Tau regulates its binding to microtubules, and abnormal phosphorylation may result in the detachment of Tau from microtubules and promote Tau aggregation.[1] Hyperphosphorylated Tau protein, the main component NFTs, is believed to be more specific to AD pathology.[5] While the roles of these phosphorylated Tau variants warrant further investigation, their rise and fall measured in CSF and plasma could be useful in tracking AD and other diseases associated with Tauopathies. This multi-faceted nature of Tau gives rise to an expansive menu of biomarkers that is very likely to continue growing, with each marker potentially offering distinct advantages reflecting clinically relevant brain pathophysiology.

Total Tau (t-Tau)

CSF t-Tau levels reflect neuronal injury and degeneration and are widely used in clinical and research settings for brain injury as well as neurodegenerative diseases, including not only classical proteinopathy like AD and amyotrophic

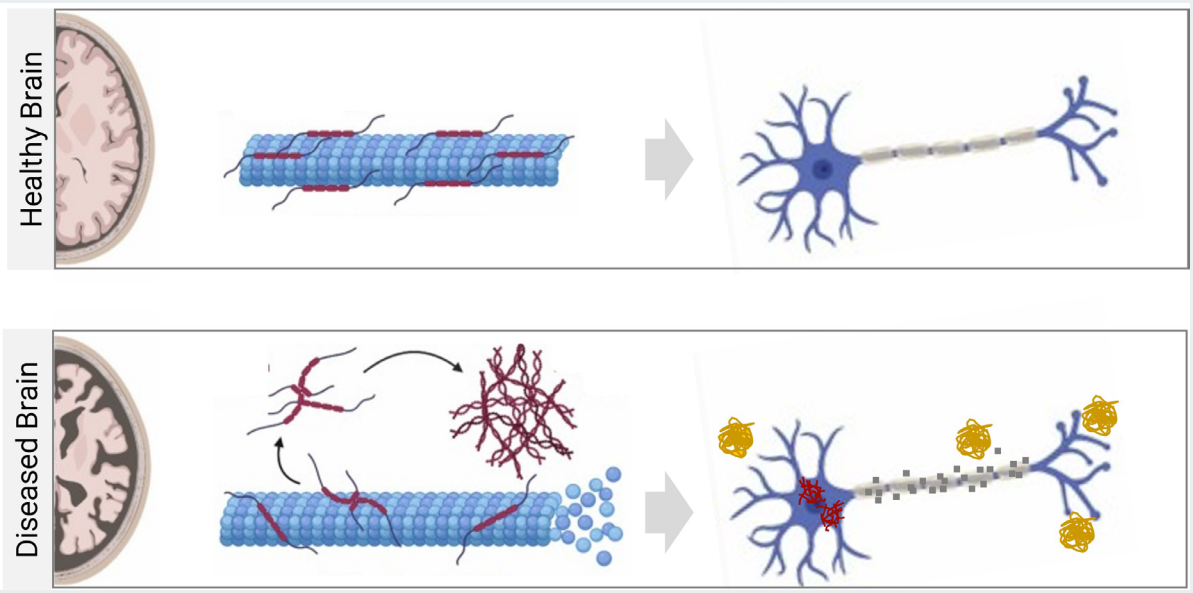

Figure 1: A schematic representation Tau protein status in (a) physiological conditions, where it binds to and stabilizes neuronal microtubules, thus maintains the normal morphology of neurons in the health brain; (b) pathological conditions, where hyperphosphorylation of Tau leads to abnormal conformational changes, detachment from microtubules, and the formation of neurofibrillary tangles (red) inside neurons. Extracellular amyloid plaques (yellow) may also present as another pathological hallmark in the diseased brain. Figure adapted from Bitra et. al.[2]

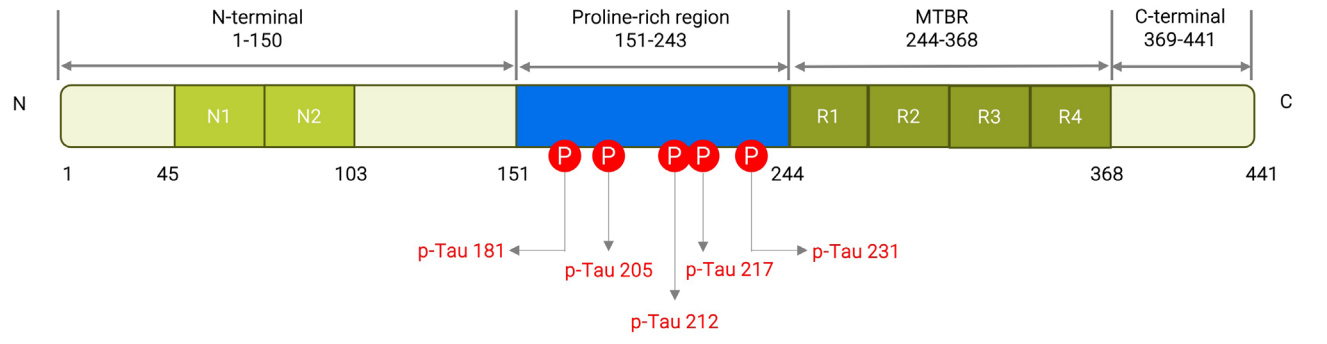

Figure 2: A schematic illustration of full-length Tau protein (2N4R Tau) in the human brain. The prominent p-Tau variants relevant in AD are highlighted in red. Figure adapted from Barbier et. al.[4]

lateral sclerosis (ALS), frontotemporal dementia (FTD), but also inflammatory disorders like multiple sclerosis (MS).[6] t-Tau represents overall Tau protein levels, encompassing all Tau isoforms and PTM variants of all tissue origin that can be detected in a given biological sample. CSF t-tau levels are elevated in patients with AD, when compared to healthy controls, and are positively associated with a more rapid disease progression.[7] However, t-Tau lacks adequate specificity for AD and plasma t-Tau levels do not correlate with CSF t-Tau, likely due to predominant peripheral sources, limiting the utility of plasma t-Tau as an AD biomarker.[8,9,10]

Phosphorylated Tau (p-Tau) species

p-Tau is a class of biomarkers that have shown better specificity for AD pathology, with superior performance than t-Tau and neurofilament light chain (NfL), another key marker for neurodegeneration, in distinguishing AD from non-AD neurodegenerative diseases.[11, 12] Plasma p-Tau levels strongly correlate with CSF t-Tau and Aβ-PET. Plasma p-Tau levels increase before insoluble Tau tangles are detectable by Tau-PET, indicating the potential for early detection of AD pathology.[13, 14, 15] Here we highlight the frontrunner p-Tau biomarkers and emerging p-Tau species for detecting and tracking AD pathophysiology.

p-Tau 181

p-Tau 181 was the first Tau phospho-epitope characterized as a plasma biomarker for AD. Elevated p-Tau 181 levels strongly correlate with the presence of AD neuropathology and have been used for predicting the progression of neurodegenerative conditions associated with AD.[12] Importantly, this biomarker can be measured in plasma and accurately predict AD pathology at least eight years prior to death, making p-Tau 181 a promising diagnostic tool.[16]

p-Tau 231

p-Tau 231 has been shown to be one of the earliest Tau epitopes to become abnormally phosphorylated across the AD continuum. It is detectable in the brains of Alzheimer's patients prior to the onset of symptoms, potentially allowing the earliest detection of AD pathophysiological changes.[17] Research has shown that p-Tau 231 has higher accuracy for predicting AD than p-Tau 181 and yields significantly fewer false positives.[18] Consequently, plasma p-Tau 231 has been actively investigated as a valuable biomarker for early disease detection.[19, 20]

p-Tau 217

p-Tau 217 has emerged as the preferable biomarker for AD diagnosis and monitoring in the single-marker context. Plasma p-Tau 217 outperforms p-Tau 181 and p-Tau 231 with higher accuracy in identifying Aβ-PET and Tau-PET positivity while exhibiting a stronger association with neurodegeneration and cognitive decline.[21, 22, 23] Both CSF and plasma p-Tau 217 levels increase before tau aggregates become detectable by Tau-PET, suggesting that plasma p-Tau217 can be used as an early Alzheimer's disease biomarker.[24, 25] Plasma p-Tau 217 has the accuracy and reliability equivalent to CSF biomarkers in differentiating AD from non-AD neurodegenerative diseases.[26, 27]

p-Tau 217 was used in the clinical trials of the TRAILBLAZER-ALZ study as a biomarker to assess treatment efficacy of donanemab (Kisunla™), a recently FDA-approved anti-amyloid treatment. Data from this study support the potential for plasma p-Tau 217 as a predictive biomarker for patient stratification, tracking disease progression and therapeutic impact.[28, 29]

p-Tau 205

Phosphorylation at threonine 205 marks a critical shift in tau biology, correlating strongly with conformational rearrangements linked to neurofibrillary tangle formation. Positioned within the epitope recognized by the AT8 antibody (Ser202/Thr205), p-Tau 205 is a key intermediate along the path from soluble tau to insoluble PHF-tau. Importantly, this marker rises later in the Alzheimer's disease trajectory compared to early-stage markers like p-Tau 217, and shows strong correlations with Braak staging, tau PET signal, and cognitive decline. Recent high-sensitivity immunoassays have enabled quantification of p-Tau 205 in CSF, serum, and plasma. These findings position p-Tau 205 as a high-value biomarker for late-stage tauopathy and for assessing the downstream impact of tau-targeted therapeutics. Moreover, p-Tau 205 shows limited correlation with amyloid pathology, offering enhanced specificity for tau aggregation over earlier markers.[30-32]

p-Tau 212

Plasma p-Tau 212 is a recently characterized phospho-epitope located at threonine 212, now resolvable as a discrete biomarker through Simoa®-based immunoassays. This marker reflects a conformational state of tau distinct from other phospho-sites such as p-Tau 181 and p-Tau 217 and is associated with early/mid-stage tau pathology, including the presence of ghost tangles and other insoluble aggregates. Notably, p-Tau 212 levels rise early in Alzheimer's disease pathogenesis and continue to increase throughout disease progression, showing strong correlation with both amyloid and tau PET positivity. Studies indicate that p-Tau 212 provides high diagnostic accuracy and captures additional variance in tau burden beyond what is explained by p-Tau 217 alone[33]. Furthermore, in Down Syndrome-associated Alzheimer's disease, p-Tau 212 rises as early as 15 years before clinical onset and correlates with amyloid PET positivity and CSF levels[57]. The ability to measure p-Tau 212 in CSF, plasma, and serum also supports its integration into scalable, blood-based screening frameworks for trial enrollment and disease monitoring. When used in tandem with BD-Tau, p-Tau 212 may further enhance identification of CNS-derived tauopathy in early disease states.

Tau Fragments

While the leading p-Tau biomarkers (p-Tau 181, p-Tau 217, p-Tau 231) are highly specific to AD, they track both amyloid and tau pathology, making it difficult to determine the contribution of Tau deposition to the plasma p-Tau signal. There is an unmet need for biomarkers specific for insoluble Tau accumulation in the brain. In addition to p-Tau 205, which has shown promise in reflecting Tau pathology more than amyloid pathology, new studies are presenting specific fragments as novel biomarkers with higher specificity for Tau aggregate deposition.

MTBR-Tau 243

The microtubule-binding region (MTBR) of Tau containing the residue 243 (MTBR-tau243) is being investigated as a new, specific biomarker for insoluble Tau aggregates. When compared with multiple key p-Tau variants (181, 217, 231, 205), MTBR-Tau243 demonstrates the strongest association with Tau-PET and cognition and least association with amyloid-PET, highlighting its superior specificity to Tau pathology. MTBR-Tau243 increases longitudinally with insoluble Tau aggregates and, in combination with p-Tau 205, explains most of the variance in Tau pathology observed with Tau-PET imaging, making it a promising biomarker reflecting Tau aggregates.[34] This will be particularly valuable for the development of emerging Tau-targeting AD treatments.

NTA-Tau

Recognizing that serval of the high-performing Tau assays (phosphorylated or non-phosphorylated) share an N-terminally directed strategy in the assay design – targeting Tau fragments containing the N terminus. Scientists at the University of Gothenburg devised a new assay that measures N-terminal containing Tau fragments (NTA-Tau).[35] Early data indicate a close association of plasma NTA-Tau with in vivo Tau tangle deposition in AD, and its downstream effects, including cortical thickness and cognition. NTA-Tau holds promise as a new biomarker for a surrogate measure of tangle accumulation and its downstream effects, providing valuable insight in disease monitoring and treatment outcome assessment.[36]

Brain-derived Tau (BD-Tau)

A Novel Plasma Biomarker for AD-specific Neurodegeneration and Clinical Outcome Prediction after sTBI and AIS

Brain-derived Tau (BD-Tau) refers to Tau proteins expressed by the central nervous system (CNS). BD-Tau primarily comprises of low molecular weight (M.W.) isoforms that lack the large peptide insert from exon 4a, a feature of the main isoform expressed in peripheral tissues also known as "Big Tau" (Figure 3).[37, 38] The Simoa® BD-Tau assay, developed based on a method pioneered by scientists at the University of Gothenburg, enables selective measurement of BD-Tau in blood by targeting the small peptide spanning the junction between exons 4 and 5 unique to CNS Tau forms.[38] This innovative method has enabled characterization of BD-Tau as a promising blood-based biomarker with unique brain specificity for neurological disorders.

BD-Tau for Alzheimer's Disease (AD)

Unlike plasma t-Tau, plasma BD-Tau levels strongly correlate with CSF t-Tau and track with amyloid pathophysiology. Plasma BD-Tau outperforms t-Tau and NfL in distinguishing AD-specific neurodegeneration from other dementias, with a potential to predict risks for short-term cognitive decline in AD individuals. Additionally, compare to NfL, blood BD-Tau levels have shown to be less susceptible to age, renal function, APOE genotype, and other comorbidities, suggesting blood BD-Tau may help improve the accuracy in the stratification of individuals in heterogenous populations.[38, 39, 40]

BD-Tau for Severe Traumatic Injury (sTBI) and Acute Ischemic Stroke (AIS)

Higher plasma BD-Tau levels at admission and day 7 post-sTBI have been shown to track with unfavorable clinical outcomes. In a 1-year post-sTBI follow-up study, BD-Tau exhibited a slower clearance trajectory in blood than other neuronal injury biomarkers like NfL, with a substantial amount of BD-Tau remaining a year after the event.[41] This slow clearance makes plasma BD-Tau a promising biomarker for the clinical monitoring of outcomes and recovery for sTBI patients.

Multiple recent studies highlight the potential of plasma BD-Tau as a novel biomarker for improving the clinical outcome prediction of AIS. It has been shown that plasma BD-Tau levels highly correlate with cerebral infarct volumes, a key indicator of brain tissue damage and stroke severity. Overall, these data suggest the potential of plasma BD-Tau as an accessible, cost-effective biomarker for assessing acute brain injury upon AIS and for improving the prognostic accuracy.[42, 43, 44]

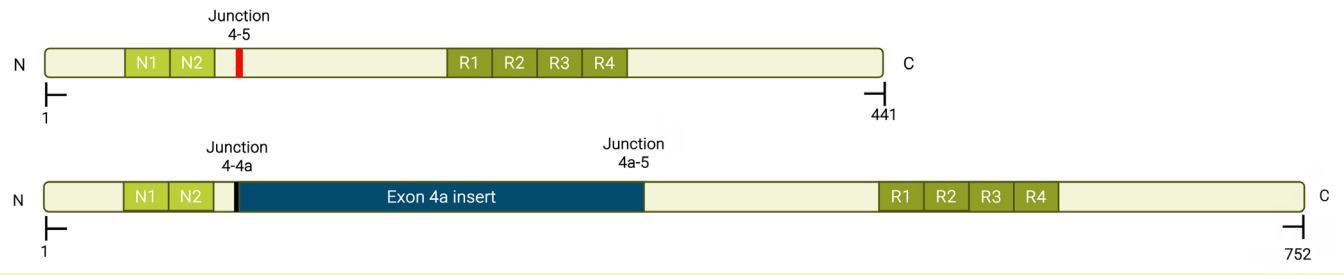

Figure 3: BD-Tau versus high M.W. peripheral tau isoforms. Schematic representation of the full-length Tau protein expressed in CNS e.g. BD-Tau (upper) and full-length Tau expressed in the periphery that contained the extra segment encoded by exon 4a (lower). The red box in BD-Tau represents the small peptide, spanning the junction between the regions encoded by exons 4 and 5, recognized by Simoa® BD-Tau assays. This figure is adapted from Gonzalez-Ortiz F, et al.[38]

Single Marker vs. Multi-marker Approach

While single-marker assays targeting an individual Tau form alone, such as p-Tau 217, may offer excellent performance in detecting AD pathology, it is increasingly common to analyze several markers for both core pathologies (amyloid and Tau) and additional pathological processes, such as inflammation, neuroaxonal degeneration, and astrocytosis. Analyzing multiple markers from a single sample source could help provide more precise characterization of diseases, disease subtypes, stages, and treatment responses.[45, 46] Ratios of phosphorylated versus non-phosphorylated peptides, and even hybrid ratios (Tau and Aβ) are being utilized for diagnostic, staging, and prognostic criteria.[47]

It is believed that ratios allow for normalization of individual variations in Tau biomarkers production and clearance, as well as for sample volume, which can also alter biomarker concentrations. In addition, Tau exists in the form of fragments that contain a mix of N-terminal and mid-region domains, suggesting that accurate quantification may benefit from detecting different regions of the same marker.[48]

Methods for Tau Biomarker Detection

Tau-PET, a non-invasive in-situ imaging technique, which reveals the presence, location, and density of Tau tangles in the brain, remains the gold standard for confirming neurofibrillary tangle pathology of AD. However, Tau-PET is an expensive procedure that requires specialized equipment and is therefore not well suited for longitudinal monitoring or diagnostic screening. Advent in high-sensitivity analytical platforms, primarily immunoprecipitation mass spectrometry **(IP-MS)** and **automated advanced immunoassay** technologies like Simoa®, has enabled reliable measurements of CSF and plasma Tau and other neurology biomarkers, making blood tests increasingly commonplace for AD research and disease management.

IP-MS techniques offer high sensitivity and specificity, delivering the best accuracy in detecting AD pathology in recent cross-platform assay comparison studies for p-Tau 217. Meanwhile, all comparator assays demonstrate high ability to detect abnormal Amyloid-PET and Tau-PET.[27,50]

IP-MS allows simultaneous quantification of multiple Tau forms, facilitating characterization of differential associations of different Tau forms with AD pathology. A recent study employed IP-MS to analyze 6 p-Tau and 2 non-phosphorylated Tau species, reporting p-Tau 217, p-Tau 231 and p-Tau 205 being the plasma Tau forms that best reflect AD-related brain changes. This study also finds distinct emergences of various p-Tau abnormalities along the disease course and correlations with AD features—amyloid and Tau. While IP-MS is a powerful technology for plasma AD biomarker detection, the technology is complex and expensive, with low throughput and high operational cost, limiting its broad clinical implementation.[49, 50]

Immunoassays represent the most accessible and scalable method for measuring both CSF- and blood-based Tau. Early attempts with conventional ELISA were challenged in sensitivity for plasma Tau biomarker detection, especially for p-Tau and other sub-forms of Tau as their concentrations in blood are extremely low. With up to 1000-fold greater sensitivity over conventional ELISA, the ultra-sensitive **Simoa® digital immunoassay technology** has reshaped the landscape of biomarker detection, by pioneering ultra-sensitive assays solutions in neurology. Simoa® has been instrumental in the discovery and research of the various Tau biomarkers.

Tau Biomarkers in Alzheimer's Diagnosis and Treatment

Plasma biomarkers represent an attractive avenue for early diagnosis of AD due to the non-invasive and cost-effective nature of blood tests. Several Tau biomarkers, including p-Tau 181, p-Tau 217, and p-Tau 231 are being used in clinical trials for developing treatments for AD.[52] It is only a matter of time before Tau biomarkers become part of routine clinical diagnostics and even screening at presymptomatic stages. Further studies are required to better understand the performance of these biomarkers measured by different assays and platforms in different clinical contexts and across disease stages. It is also important to delineate the influences of comorbidities (such as kidney disease[53]) on the plasma levels of Tau biomarkers. Longitudinal studies are essential to explore the correlations between plasma Tau biomarkers to Tau-PET imaging, neurodegeneration, and cognition. Additionally, investigations into intra-individual biomarker variability are critical to determine clinically relevant thresholds.

Tau biomarkers are crucial for monitoring changes in response to treatments. With the approval of the anti-

amyloid antibody drug donanemab (Kisunla™) in the United States and the United Kingdom in 2024, antibody-based therapies for AD have gained significant attention. The clinical study of donanemab showed a significant reduction in levels of p-Tau 217 and glial fibrillary acidic protein (GFAP) plasma biomarkers in patients with early symptomatic AD, demonstrating the utility of Tau biomarkers in assessing the efficacy of AD treatments.[54]

In addition to anti-amyloid treatments, Tau-targeting therapies, including vaccines and antibody therapies, represent one of the most active fields of AD therapeutic research.[55] A recent Phase 2a study suggests that Tau-targeting antibodies, such as bepranemab, show potential for slowing Tau pathology progression in AD, particularly in patients with mild cognitive symptoms.[56] However, challenges remain in identifying the optimal patient population and treatment timing, underscoring the need for clinically relevant biomarkers. Additionally, combinations of Tau- and amyloid-targeting therapies are being explored, with trials already underway.

Into the Future: Powering Biomarker Discovery, Assay Innovation, and Biomarker Translation in Alzheimer's and Beyond with Simoa®

The unprecedented progress in Tau biomarker research, powered by the advancements in ultra-sensitive quantification methods, promises a future where Alzheimer's disease can be detected earlier and with greater precision. This will ultimately lead to more effective management and treatment, reducing the societal burden of dementia care.

Today, Quanterix offers the most extensive and cutting-edge biomarker menu on the Simoa platform for AD and neurology research. Trusted by scientists around the world, the Simoa® technology has been cited in over 3000 peer-reviewed studies. As the field continues to grow, new insights into the specific roles and functions of existing and emerging Tau forms will drive further research into their utility as valuable biomarkers for clinical use. With deep expertise in ultra-sensitive biomarker assay development and global leadership in biomarker innovation, Quanterix remains at the forefront of revolutionizing biomarker research for Alzheimer's disease and beyond.

Explore Quanterix Simoa® Technology for Neurology Biomarker Detection

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