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LUMIPULSE® BLOOD TEST FOR ALZHEIMER'S DISEASE DIAGNOSIS: A REVIEW OF BIOMARKER INNOVATION AND CLINICAL APPLICATIONS

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ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, memory loss, and behavioural changes, and it remains the leading cause of dementia worldwide. Despite its growing prevalence, early and accurate diagnosis continues to pose significant clinical challenges. Current diagnostic standards, such as cerebrospinal fluid (CSF) biomarker analysis and amyloid PET imaging, although reliable, are invasive, expensive, and not easily accessible in all clinical settings. The recent development and FDA clearance of the Lumipulse G β-Amyloid Ratio and pTau217/β-Amyloid 1-42 plasma tests mark a significant advancement in the diagnostic landscape. Based on chemiluminescent enzyme immunoassay (CLEIA) technology, the Lumipulse platform enables the quantification of key plasma biomarkers including Aβ1–42, Aβ1–40, and phosphorylated tau proteins, which strongly correlate with AD pathology. Clinical studies, including NIH-supported validation cohorts, have demonstrated high diagnostic accuracy, with strong agreement between plasma biomarkers and traditional CSF and PET measures. This minimally invasive, high-throughput blood test offers an accessible alternative to current diagnostic methods, facilitating early detection and improving the potential for timely intervention. While limitations such as inter-laboratory variability and the need for further population-specific validation persist, the Lumipulse test holds immense promise in transforming Alzheimer's disease diagnosis and guiding clinical decision-making in both primary and specialized care settings.

INTRODUCTION

Alzheimer's disease is a progressive neurological condition that primarily impacts memory, cognitive function, and behaviour, ultimately leading to an inability to carry out everyday tasks. It is the most prevalent cause of dementia, affecting over five million Americans, a figure projected to rise to nearly 14 million by 2050. This disorder is a major contributor to disability and mortality, yet current methods for diagnosis are inadequate [1]. Alzheimer's disease progresses for several years before symptom become apparent, but the scarcity of accessible diagnostic tools often results in patients not being diagnosed until the disease has significantly advanced, at which point there are few effective treatment options available. The presence of amyloid plaques in the brain is a key indicator of Alzheimer's disease. These plaques can be identified and visualized through amyloid positron emission tomography (PET) brain scans; often years before any clinical symptoms appear, assisting in the diagnosis of Alzheimer's disease. However, PET scans are expensive, time-intensive, and involve radiation exposure for patients. The Lumipulse G β-Amyloid Ratio

(1-42/1-40) offers an alternative to these current standards for determining amyloid-pathology. The β-Amyloid Ratio test measures the concentrations of β-Amyloid 1-42 and β-Amyloid 1-40 in the CSF to calculate a numerical ratio as a proxy for the presence of β-Amyloid plaque in the brain [1-3].

Lumipulse test-what is it and how it works?

The Lumipulse G β-Amyloid Ratio (1-42/1-40) test is an accurate, minimally invasive, accessible measure of β-Amyloid that can detect the formation of amyloid plaques early in the disease. It is intended for use in adult patients aged 55 years and older presenting with cognitive impairment who are being evaluated for Alzheimer's disease and other causes of cognitive decline. Low levels of Aβ42, or Aβ42/Aβ40 ratio, are suggestive of the brain Aβ pathology, and high pTau levels are indicative of pathologic changes correlated with pTau accumulation in brain tissue. Since the neurodegenerative process begins years before the onset of symptoms, the use of CSF biomarkers is essential for identifying the disease at the very early stages, when the chances of preventing neuronal loss by disease-modifying treatments are greater. The Lumipulse test offers a simpler and less-invasive alternative. Using Fujirebio Diagnostics' (PA, USA) fully automated Lumipulse G1200 instrument system based on chemiluminescent enzyme immunoassay (CLEIA) technology, the test works by measuring two proteins in blood plasma-pTau217 and β-Amyloid 1-42-and calculating their ratio, which correlates strongly with the presence of plaques [4,5].

How are blood samples collected and processed: Blood samples are collected in EDTA-K2 tubes and subsequently centrifuged (2000 rpm × 10 min, 4ºC) within 2 h after extraction. Plasma must be aliquoted and stored at -80ºC until analysis. CSF samples are obtained through lumbar puncture, and are also centrifuged, aliquoted and stored at -80ºC until analysis. Blood and CSF samples are collected simultaneously. All plasma samples are measured in the Lumipulse fully-automated platform G600II using commercially available kits (Fujirebio) for pTau181, Aβ1-42 and Aβ1-40 with the same lot of reagents. Plasma pTau217 is analyzedin another aliquot of the same samples using a novel assay developed by Fujirebio. On the day of the analysis, plasma samples are brought to room temperature, mixed thoroughly, centrifuged for 5 min at 2000 g, and subsequently transferred to specific cuvettes for analysis in the Lumipulse platform.CSF markers Aβ1–42, Aβ1–40, pTau181 and tTauare used in the diagnostic assessment of patients and measured in routine runs scheduled twice a month throughout the year following previously reported methods [6-8].

NIH-supported studies on Lumipulse test performance Methods: The National Institutes of Health (NIH) has played a significant role in supporting independent validation studies of blood-based biomarkers, including those utilized in the Lumipulse platform for Alzheimer's disease detection. A retrospective exploratory cohort of 138 individuals (22 neurological controls [NC], 72 MCI, and 44 AD dementia patients) was included. Data regarding baseline CSF concentrations of Aβ42, Aβ40, t-Tau, and p-Tau181 was available and used to establish the presence of AD brain pathology. Baseline Aβ42, Aβ40, and p-Tau181 concentrations were determined in stored plasma samples using high-throughput fully automated LUMIPULSE assays. Progression from MCI to AD dementia was evaluated during follow-up (mean 6.4 ± 2.5 years). Moreover, a prospective validation cohort of 72 individuals with memory complaints underwent AD biomarker quantification, closely mirroring typical clinical practice. This cohort aimed to confirm the study's main findings.

Results: In the exploratory cohort, correlations between CSF and plasma were moderate for p-Tau181 ($\rho = 0.61$, $p < 0.001$) and weak for Aβ42/Aβ40 ratio ($\rho = 0.39$, $p < 0.001$). Plasma p-Tau181 and p-Tau181/Aβ42 concentrations were significantly increased while Aβ42/Aβ40 was significantly decreased ($p < 0.001$) in patients with AD dementia and prodromal AD, as well as in individuals with CSF abnormal amyloid concentrations (A +). Plasma p-Tau181 showed a robust performance in differentiating patients clinically diagnosed as AD (AUC = 0.89; 95% CI 0.83-0.94); A + vs. A - (AUC = 0.84, 95% CI 0.77-0.91) and in predicting conversion to AD dementia in MCI

patients (AUC = 0.89, 95% CI 0.81-0.96). When tested in the validation cohort, plasma p-Tau181 displayed 83.3% of the overall percentage of agreement according to amyloid status.

Conclusion: The results show that the measurement of p-Tau181 in plasma has great potential as a non-invasive prognostic screening tool for implementation in a clinical setting [8,9].

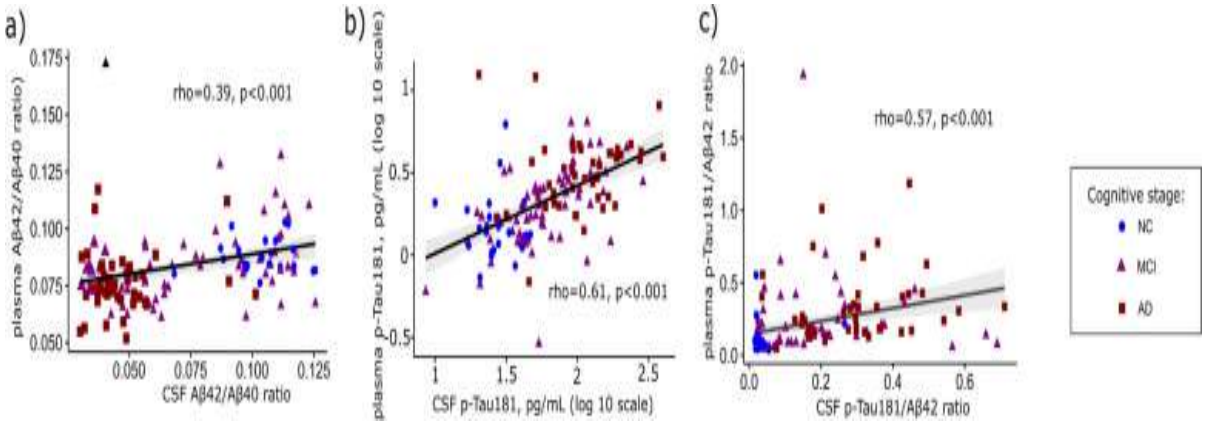

Figure 1: Associations between CSF amyloid and phosphorylated Tau with corresponding plasma concentrations in the exploratory cohort. A CSF and plasma Aβ42/Aβ40 ratio. B CSF and plasma p-Tau181 concentrations. C CSF and plasma p-Tau181/Aβ42 ratio. Graphs are presented with a logarithmic transformed axis, except for the ratios. Data displays individual values with mean regression and 95% prediction lines, with shapes corresponding to the cognitive stage (• NC, ▲ MCI, and ■ AD). Spearman correlation coefficients and *p*-values are presented for each graph. *Abbreviations*: Aβ, amyloid beta; AD, Alzheimer's disease dementia; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; NC, neurological control; p-Tau181, phosphorylated tau protein in the position 181.

FDA approval for first blood test to aid Alzheimer's diagnosis The US Food and Drug Administration (FDA; MD, USA) has approved the first blood test designed to aid in diagnosing Alzheimer's disease. Cleared on May 16 2025, the Lumipulse G pTau217/β-Amyloid 1-42 Plasma Ratio offers clinicians a faster, less invasive alternative to traditional diagnostic methods by detecting amyloid plaque accumulation in the brain-one of the hallmarks of Alzheimer's. "Alzheimer's disease impacts too many people, more than breast cancer and prostate cancer combined," said FDA Commissioner Martin A. Makary, M.D., M.P.H. "Knowing that 10% of people aged 65 and older have Alzheimer's, and that by 2050 that number is expected to double, I am hopeful that new medical products such as this one will help patients" [10,11].

Diagnostic accuracy and clinical considerations: The new blood test can reliably predict the presence or absence of amyloid pathology associated with Alzheimer's disease at the time of the test in patients who are cognitively impaired. The test is intended for patients presenting at a specialized care setting with signs and symptoms of cognitive decline. The results must be interpreted in conjunction with other patient clinical information. The risks associated with the Lumipulse G pTau217/ß-Amyloid 1-42 Plasma Ratio are mainly the possibility of false positive and false negative test results. A positive Lumipulse G β-amyloid Ratio (1-42/1-40) test result is consistent with the presence of amyloid plaques, like what would be seen in a PET scan. A negative result is consistent with a negative amyloid PET scan result. A negative test result reduces the likelihood that a patient's cognitive impairment is due to Alzheimer's disease, enabling physicians to pursue other causes of cognitive decline and dementia. The test is not intended as a screening or stand-alone diagnostic assay. There is also the possibility that a positive test result could be seen in patients with other types of neurologic conditions, as well as in older cognitively healthy people, which underscores the importance of using this test in conjunction with other clinical evaluations [12-14].

Advantages of plasma Lumipulse test: Lumipulse plasma p-tau181 assay run on a fully-automated and high-throughput platform discriminated AD with a high degree of accuracy. It is associated with CSF and PET AD biomarkers, and predicted AD-related measures of prospective cognitive and functional decline. While several prototype assays have been developed to measure plasma p-tau in clinical

and research settings, many are not yet commercially available - a constraint limiting widespread implementation. The Lumipulse plasma p-tau181 is a high-throughput, fully-automated, highly scalable, and accessible assay that is potentially useful for widescale early detection, diagnosis, and therapeutic monitoring of AD. The invasiveness of lumbar punctures underlines the need for more scalable, standardized, and high-throughput methods for the transition from CSF to blood-based markers (Plasma Lumipulse Test) of AD pathology [14,15]. **Limitations of plasma Lumipulse test:** The Lumipulse plasma p-tau181 assay for AD, this study has several limitations. First, multi-site comparisons will need to be performed to determine the site-to-site variability in the assay. For example, it is unlikely that it will perform well at other centers or while examining other cohorts, and it is instead more likely that center-specific cutoffs will be needed. Secondly, it will be important to assess associations between baseline plasma p-tau181 concentration and the rate of conversion to AD dementia. In this regard, however, implementation of plasma p-tau181 may help alleviate some of the barriers to the inclusion of more diverse populations. For example, despite recent advances in blood-based biomarkers, the recommended gold standard for AD diagnosis remains through amyloid and tau PET neuroimaging and the associated cost. and the required expertise for PET are often prohibitive. In these ways, plasma p-tau181 measurement may serve to improve recruitment efforts to diversify research in support of expanding equitable medicine [15-17].

CONCLUSION: The early and accurate diagnosis of Alzheimer's disease remains a critical unmet need in neurology, with major implications for patient care, clinical research, and public health. Traditional diagnostic tools like amyloid PET scans and CSF analysis, while effective, are often limited by high costs, invasiveness, and accessibility challenges. The emergence of blood-based biomarkers-particularly through the development of the Lumipulse G β-Amyloid Ratio and pTau217 assays-represents a transformative step in Alzheimer's diagnostics. The Lumipulse platform leverages chemiluminescent enzyme immunoassay (CLEIA) technology to provide a highly sensitive, fully automated, and scalable solution for detecting key pathological markers such as Aβ42, Aβ40, and phosphorylated Tau (pTau181 and pTau217). Validated through multiple NIH-supported and independent clinical studies, these biomarkers have demonstrated strong correlations with established CSF and PET imaging indicators, and have shown promise in predicting disease progression from mild cognitive impairment to full-blown dementia.

With FDA approval and the ability to provide rapid, non-invasive, and cost-effective diagnostic support, the Lumipulse test opens new avenues for earlier detection, patient stratification, and timely intervention. Importantly, it offers the potential to democratize access to Alzheimer's diagnostics—reaching underrepresented populations and improving equity in care delivery. While limitations such as inter-laboratory variability, cohort-specific thresholds, and false positives remain, ongoing multicenter studies and technological refinements are expected to address these gaps.

Table 1: Comparison of Lumipulse test with other diagnostic methods for Alzheimer's disease

Diagnostic Method	Sample Type	Invasiveness	Biomarkers Measured	Technology Used	Turnaround Time	Cost
Lumipulse G Plasma Test	Blood (Plasma)	Low	pTau217, β-Amyloid 1–42	CLEIA (Automated Immunoassay)	Fast (Few hours)	Moderate
CSF Biomarker Analysis	Cerebrospinal Fluid	High	Aβ1–42, Aβ1–40, tTau, pTau	Immunoassay / ELISA	1–3 days	Moderate–High
Amyloid PET Imaging	Imaging (Brain)	Moderate	Amyloid Plaques	PET Scan	Several hours	Very High
MRI (Structural Brain Imaging)	Imaging (Brain)	None	Brain Atrophy (especially hippocampus)	Magnetic Resonance Imaging	1–2 hours	High
Neuropsychological Testing	Behavioural Assessment	None	Cognitive domains (memory, language, etc.)	Paper-based / Digital tools	1–2 hours	Low

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Conflicts of Interest: The authors declare no conflict of interest.

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