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The pTau217/Aβ_{1-42} plasma ratio: The first FDA-cleared blood biomarker test for diagnosis of Alzheimer's disease

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SUMMARY: As the most prevalent form of dementia, Alzheimer's disease (AD) represents a major public health challenge. Early diagnosis is crucial to delaying disease progression, and yet the gold standard for detection of biomarkers — cerebral positron emission tomography (PET) imaging and cerebrospinal fluid biomarker analysis — is constrained by invasiveness, high costs, and limited accessibility. On May 16, 2025, the FDA granted its first clearance to the Lumipulse G blood test, which utilizes the plasma pTau217/Aβ_{1-42} ratio, for the diagnosis of amyloid plaques in symptomatic patients age 55 or older. In clinical validation, concordance rates with amyloid PET brain scans/the results of cerebrospinal fluid biomarker detection were 91.7% (positive) and 97.3% (negative). Similar blood-based assays have previously been approved in Japan (HISCL™ A$\beta_{42/40}$), the United Kingdom (PrecivityAD2™), and China. While concerns regarding false-positive/false-negative rates necessitate continued attention and their role as adjunctive diagnostic tools requires integration with comprehensive clinical assessment and other tests, the rapid development and regulatory clearance of these blood-based biomarker assays undeniably offer promising prospects for transforming the diagnostic and therapeutic paradigm for AD.

Keywords: β Amyloid 1-42, Lumipulse G, Alzheimer's disease, PrecivityAD2, A$\beta_{42/40}$

Alzheimer's disease (AD) is a central nervous system degenerative disease that typically manifests with an insidious onset and is characterized by a slow progression, representing the most common dementia subtype (*1*). Clinically, the disease presents with memory impairment and cognitive decline, accompanied by behavioral and psychiatric alterations. These symptoms progressively compromise patients' ability to perform everyday activities and ultimately severely impact their quality of life and impose a substantial caregiving burden on their families. According to statistics from the World Health Organization, the global population living with dementia is projected to increase from 55 million in 2019 to 139 million by 2050, with AD accounting for approximately 60-70% of these cases (*2*). Currently, the treatment options for AD are limited, and their efficacy is not satisfactory (*3-5*). As the population continues age, the number of AD cases will continue to increase, creating one of the most serious global health crises.

AD exhibits a continuum of pathogenesis, with pathological alterations potentially occurring decades prior to the manifestation of clinical symptoms. Early diagnosis and timely intervention are therefore critical to delaying or even halting disease progression (*3,6*). The current gold standard for AD biomarker diagnosis relies on positron emission tomography (PET) brain scans demonstrating β-amyloid or Tau positivity, coupled with cerebrospinal fluid (CSF) analysis revealing decreased Aβ_{1-42} levels alongside elevated levels of total Tau and phosphorylated Tau (pTau) protein. These diagnostic modalities have demonstrated substantial reliability, but they also have significant limitations: CSF biomarker collection involves considerable invasiveness and patient discomfort, while PET imaging remains prohibitively expensive. These constraints restrict their widespread clinical implementation, thereby impeding early screening and diagnosis of AD. Blood-based biomarker detection has emerged as a promising focus of research to overcome these limitations. Nevertheless, challenges in analytical sensitivity and specificity have historically prevented blood tests from replacing cerebral PET imaging and CSF biomarker analysis as the clinical diagnostic standard for AD.

On May 16, 2025, the US Food and Drug Administration (FDA) granted its first clearance for an *in vitro* blood-based diagnostic test for AD (*7*). This test aids in AD diagnosis by detecting the plasma ratio of pTau217 to Aβ_{1-42} and is intended for early

identification of amyloid plaques associated with AD in the brains of adult patients age 55 and older who exhibit AD-related symptoms. Unlike invasive lumbar puncture for CSF collection, this technique requires only peripheral blood sampling, offering a less invasive and more patient-friendly approach. The blood test is considered substantially equivalent to the previously approved Lumipulse G assay for the $A\beta_{1-42}/A\beta_{1-40}$ ratio in CSF samples. The clearance was based on a prior clinical study involving 499 plasma samples from adults with cognitive impairment (*7*). The study utilized the Lumipulse G assay to measure the plasma pTau217/$A\beta_{1-42}$ ratio and compared results with amyloid PET scans or CSF testing. Clinical data showed that 91.7% of individuals with positive Lumipulse G results were confirmed to be amyloid-positive by PET or CSF testing, while 97.3% of those with negative Lumipulse G results had negative amyloid PET or CSF outcomes (*7*). Fewer than 20% of the 499 tested patients had indeterminate Lumipulse G results. The primary risks of the Lumipulse G pTau217/$A\beta_{1-42}$ plasma ratio test include the potential for false-positive and false-negative results. A critical point worth mentioning is that this test is not intended for screening purposes and should not serve as the sole diagnostic criterion. Treatment decisions must incorporate comprehensive clinical evaluation and/or supplementary test results for integrated assessment.

Blood biomarker diagnostic tests for AD have previously been cleared in other countries. HISCL™ β Amyloid 1-42 and HISCL™ β Amyloid 1-40 assay kits, which aid in identifying brain Aβ deposition by calculating the plasma $A\beta_{42}/A\beta_{40}$ ratio, have been cleared in Japan. Clinical studies demonstrate that this test has good sensitivity and specificity, with an area under the curve of 0.895, comparable to PET scans and CSF testing results (*8*). Another AD blood biomarker test, the PrecivityAD2™ test, received medical device certification from the Medicines and Healthcare products Regulatory Agency in the United Kingdom in February 2025 (*9*). Clinical research has shown that this test has a negative predictive value (NPV) of 92% and a positive predictive value (PPV) of 91%, positioning it as a potential alternative to CSF testing and PET scans (*10*). In addition, several blood biomarker-based AD diagnostic kits have also received marketing approval in China.

The recent FDA clearance of the Lumipulse G pTau217/$A\beta_{1-42}$ plasma ratio assay, alongside the progressive regulatory clearance of similar blood-based biomarker tests in countries including Japan, the United Kingdom, and China, represents a significant advancement in the area of non-invasive blood diagnostics for AD. While concerns regarding false-positive/false-negative rates necessitate continued attention and their established role as adjunctive diagnostic tools requires integration with comprehensive clinical assessment and other tests, the rapid development and regulatory clearance of these blood-based biomarker assays undeniably offer promising prospects for transforming the diagnostic and therapeutic paradigm for AD.

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