



This is a repository copy of *The potential clinical value of plasma biomarkers in Alzheimer's disease*.

White Rose Research Online URL for this paper:  
<https://eprints.whiterose.ac.uk/203461/>

Version: Published Version

---

**Article:**

Blennow, K., Galasko, D., Perneczky, R. [orcid.org/0000-0003-1981-7435](https://orcid.org/0000-0003-1981-7435) et al. (7 more authors) (2023) The potential clinical value of plasma biomarkers in Alzheimer's disease. *Alzheimer's & Dementia*, 19 (12). pp. 5805-5816. ISSN 1552-5260

<https://doi.org/10.1002/alz.13455>

---

**Reuse**

This article is distributed under the terms of the Creative Commons Attribution (CC BY) licence. This licence allows you to distribute, remix, tweak, and build upon the work, even commercially, as long as you credit the authors for the original work. More information and the full terms of the licence here:  
<https://creativecommons.org/licenses/>

**Takedown**

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing [eprints@whiterose.ac.uk](mailto:eprints@whiterose.ac.uk) including the URL of the record and the reason for the withdrawal request.



[eprints@whiterose.ac.uk](mailto:eprints@whiterose.ac.uk)  
<https://eprints.whiterose.ac.uk/>

## REVIEW ARTICLE

## The potential clinical value of plasma biomarkers in Alzheimer's disease

Kaj Blennow<sup>1,2</sup> | Douglas Galasko<sup>3</sup> | Robert Perneczky<sup>4,5,6,7,8</sup> |  
 Frances-Catherine Quevenco<sup>9,†</sup> | Wiesje M. van der Flier<sup>10,11,12</sup> | Akin Akinwonmi<sup>9</sup> |  
 Margherita Carboni<sup>9</sup> | Alexander Jethwa<sup>13</sup> | Ivonne Suridjan<sup>9</sup> |  
 Henrik Zetterberg<sup>1,2,14,15,16,17</sup>

<sup>1</sup>Institute of Neuroscience and Physiology, Department of Psychiatry and Neurochemistry, Sahlgrenska Academy, University of Gothenburg, Mölndal, Sweden

<sup>2</sup>Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden

<sup>3</sup>Department of Neurosciences, University of California, San Diego, La Jolla, California, USA

<sup>4</sup>Department of Psychiatry and Psychotherapy, University Hospital of Munich, Munich, Germany

<sup>5</sup>German Center for Neurodegenerative Diseases (DZNE), Munich, Germany

<sup>6</sup>Munich Cluster for Systems Neurology (SyNergy), Munich, Germany

<sup>7</sup>Sheffield Institute for Translational Neuroscience (SITraN), University of Sheffield, Broomhall, Sheffield, UK

<sup>8</sup>Ageing Epidemiology (AGE) Research Unit, School of Public Health, Imperial College London, London, UK

<sup>9</sup>Roche Diagnostics International Ltd, Rotkreuz, Switzerland

<sup>10</sup>Department of Neurology, Alzheimer Centre Amsterdam, Amsterdam UMC, Amsterdam, The Netherlands

<sup>11</sup>Amsterdam Neuroscience, Neurodegeneration, Amsterdam UMC, Amsterdam, The Netherlands

<sup>12</sup>Department of Epidemiology and Data Science, Amsterdam UMC, Amsterdam, The Netherlands

<sup>13</sup>Roche Diagnostics GmbH, Penzberg, Germany

<sup>14</sup>UK Dementia Research Institute, UCL, London, UK

<sup>15</sup>Department of Neurodegenerative Disease, UCL Institute of Neurology, London, UK

<sup>16</sup>Hong Kong Center for Neurodegenerative Diseases, Hong Kong Special Administrative Region, Hong Kong, China

<sup>17</sup>Wisconsin Alzheimer's Disease Research Center, University of Wisconsin School of Medicine and Public Health, University of Wisconsin-Madison, Madison, Wisconsin, USA

## Correspondence

Ivonne Suridjan, Roche Diagnostics  
 International Ltd, Forrenstrasse 2, 6343  
 Rotkreuz, Switzerland.  
 Email: [ivonne.suridjan.ch@gmail.com](mailto:ivonne.suridjan.ch@gmail.com)

<sup>†</sup>Affiliation during article conception and development.

## Abstract

**INTRODUCTION:** Many people with cognitive complaints or impairment never receive an accurate diagnosis of the underlying condition, potentially impacting their access to appropriate treatment. To address this unmet need, plasma biomarker tests are being developed for use in Alzheimer's disease (AD). Plasma biomarker tests span various stages of development, including in vitro diagnostic devices (or tests) (IVDs), laboratory-developed tests (LDTs) and research use only devices (or tests) (RUOs). Understanding the differences between each test type is important for appropriate implementation into the AD diagnostic pathway and care continuum.

This is an open access article under the terms of the [Creative Commons Attribution](https://creativecommons.org/licenses/by/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2023 The Authors. Alzheimer's & Dementia published by Wiley Periodicals LLC on behalf of Alzheimer's Association.

**METHODS:** Authors reviewed scientific literature (PubMed, meeting abstracts and presentations, company press releases and websites) on AD plasma biomarkers.

**RESULTS:** This article defines IVDs, LDTs, and RUOs, discusses potential clinical applications and highlights the steps necessary for their clinical implementation.

**DISCUSSION:** Plasma biomarkers could revolutionize many areas of the AD diagnostic pathway and care continuum, but further research is needed.

#### KEYWORDS

Alzheimer's disease, diagnosis, diagnosis pathway, diagnostic test, plasma biomarkers, triage tool

#### HIGHLIGHTS

- There is a need for a minimally invasive Alzheimer's disease (AD) diagnostic tool.
- AD plasma biomarker tests exist at various stages of commercial development.
- Understanding the development stage of a test is important for its appropriate use.
- Plasma biomarker tests could function as a triage tool to streamline AD diagnosis.
- Further steps remain before AD plasma biomarkers can be used routinely.

## 1 | INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disorder that accounts for  $\approx$  60% to 80% of dementia cases.<sup>1</sup> It is characterized by abnormal amyloid beta ( $A\beta$ ) deposition in the form of amyloid plaques ( $A\beta$  pathology), as well as neurofibrillary tangles, dystrophic neurites and neuropil threads composed of hyperphosphorylated tau proteins (tau pathology) in the brain.<sup>2</sup> Alzheimer's Disease International estimate that, on average, > 75% of people living with cognitive complaints or impairment are undiagnosed worldwide<sup>3</sup> and *post mortem* studies report misdiagnosis rates of up to 30%.<sup>4</sup> Furthermore, a meta-analysis reported that the clinical judgment of general practitioners had a sensitivity of 58% and a specificity of 89% in the diagnosis of dementia, meaning that false negative diagnoses are likely.<sup>5</sup>

Globally, there is no standardized AD diagnostic pathway.<sup>6</sup> At present, symptomatic individuals with clinical suspicion of AD undergo a combination of clinical history taking, cognitive assessments, routine laboratory tests (e.g., blood and/or urine tests), and structural brain imaging (e.g., computed tomography or magnetic resonance imaging [MRI]) to rule out other causes of cognitive complaints or impairment.<sup>7</sup> Diagnosis of AD can be supported by positron emission tomography (PET) and/or cerebrospinal fluid (CSF) biomarker analysis,<sup>7</sup> both of which are approved by the U.S. Food & Drug Administration (FDA) for the diagnosis of AD.<sup>8-11</sup> However, use of these confirmatory tests is limited due to perceived invasiveness, high costs, and lack of specialist equipment and/or clinical expertise.<sup>12</sup>

Certifying the presence of  $A\beta$  pathology in the brain *in vivo* is important for clinical decision making, particularly with the advancement of anti- $A\beta$  disease-modifying therapies (DMTs), such as aducanumab<sup>13</sup>

and lecanemab,<sup>14</sup> which are FDA approved, and donanemab,<sup>15</sup> which has shown promising results in a phase III clinical trial. These DMTs target disease pathology in symptomatic patients early in the AD continuum, so accurate and timely diagnosis is crucial,<sup>13-15</sup> the prescribing information and appropriate use recommendations of aducanumab and lecanemab indicate that the presence of amyloid pathology in the brain should be confirmed before DMT initiation.<sup>16,17</sup> As DMTs become accessible, health services are unlikely to be prepared for the influx of patients requiring diagnostic testing for AD. This highlights an urgent clinical unmet need for a cost- and time-effective, minimally invasive, and easy-to-interpret diagnostic tool that can be widely implemented.

Plasma biomarker tests could have different applications along the AD diagnostic pathway and care continuum (Box 1). Such tests could add clinical value by potentially streamlining diagnosis, improving the patient journey, and alleviating pressure on health-care systems. There are a range of plasma biomarker tests at different stages of development for use in AD research and as part of the AD diagnostic pathway and care continuum, including *in vitro* diagnostic devices (or tests; IVDs), laboratory-developed tests (LDTs; also known as in-house devices), and research use only devices (or tests; RUOs).<sup>18</sup> As IVDs, LDTs, and RUOs have different intended uses and are subject to different regulatory requirements, understanding the differences among them is vital so that they can be appropriately implemented into the AD diagnostic pathway and care continuum.

The scope of this review is to define IVDs, LDTs, and RUOs by their relative advantages and disadvantages, discuss potential clinical applications of plasma biomarkers, and highlight the steps necessary for implementation of plasma biomarker testing into the intended use population.

**BOX 1**

Current and imminent applications for plasma biomarkers in AD:

- Acting as a triage tool by ruling out symptomatic individuals with a low likelihood of A $\beta$  pathology or ruling in symptomatic individuals with a high likelihood of A $\beta$  pathology
- Enriching clinical trial populations by screening out people without A $\beta$  pathology

Potential future applications for plasma biomarkers in AD:

- Acting as a diagnostic test, replacing confirmatory PET and/or CSF biomarker analysis
- Predicting disease progression
- Monitoring disease progression and/or treatment response, including monitoring for adverse events
- Acting as a screening test for cognitively normal individuals or individuals at risk of developing AD

**RESEARCH IN CONTEXT**

1. **Systematic Review:** The authors reviewed scientific literature (PubMed, meeting abstracts and presentations, and company press releases and websites) on plasma biomarkers in Alzheimer's disease (AD). The volume of scientific literature on plasma biomarkers in AD has increased rapidly over recent years; the number of publications indexed on PubMed has doubled since 2019.
2. **Interpretation:** This article gives the literature clinical context regarding the imminent and future uses of plasma biomarkers in AD, including discussing the practical differences between in vitro diagnostic devices (or tests), laboratory-developed tests, and research use only devices (or tests). It is necessary to understand these differences for plasma biomarker tests to be implemented appropriately in the clinic.
3. **Future Directions:** Further research and development are needed before patients and health-care facilities will tangibly benefit from AD plasma biomarker testing. In particular, the diagnostic performance and clinical utility of plasma biomarker tests must be assessed in large prospective studies.

**2 | DEFINING IVDs, LDTs, AND RUOS**

All three categories of biomarker test, IVDs, LDTs, and RUOs, serve their own purposes in the diagnostic field; the main differences among the three are summarized in Table 1. A summary of selected plasma biomarker tests for use in the AD diagnostic pathway is provided in Table 2.

The majority of plasma biomarker tests currently available, and in development, for use in the AD field are RUOs, so can only be used for research purposes. RUOs are devices that are in the laboratory research-based phase of development.<sup>19</sup> They are valuable tools for gathering real-world evidence on a particular biomarker or disease, supporting product development, and conducting non-clinical laboratory research, but they must not be used for clinical decision making or diagnosis and must be labeled as "for research use only."<sup>18,19</sup>

LDTs are designed, manufactured, and used in a single laboratory or laboratory network<sup>18,40</sup> and are important for accelerating research progress as they can often be developed more quickly and cheaply than IVDs because they only undergo limited analytical and clinical validation and regulatory review.<sup>40,41</sup> They can also be modified to allow for the rapid incorporation of new findings.<sup>41</sup> An inherent limitation of LDTs is that they are only designed and validated in one laboratory setting or network; therefore, if used elsewhere under different test conditions, they may produce inconsistent results, meaning that patients may be misclassified. LDTs may need to be more tightly regulated as, in recent years, an increasing number of LDTs from a variety of therapeutic areas have been marketed directly to clinicians and the general public, who may not necessarily understand the limitations of the claims made about this type of test.<sup>42</sup> There are several examples in which incorrect LDT use has resulted in patients being misclassified and either not receiving necessary treatment such as

chemotherapy, or undergoing unnecessary treatment including invasive surgery.<sup>43</sup> The PrecivityAD test (C<sub>2</sub>N Diagnostics) is an LDT that assesses the likelihood that a person has A $\beta$  pathology by quantitatively measuring the plasma A $\beta$ 42/A $\beta$ 40 ratio and combining this measurement with apolipoprotein E4 status and age to provide an AD risk score.<sup>44</sup> It is available for clinical use in 49 states in the U.S., the District of Columbia, and Puerto Rico for people experiencing cognitive impairment.<sup>27,38</sup>

In contrast to RUOs and LDTs, IVDs are commercially available tests intended to support clinical decision making. They have undergone extensive regulatory review to obtain approval, meaning that they produce reliable test results and are widely validated with respect to their analytical and clinical performance in the intended use population.<sup>18,22,20</sup> In December 2022, Sysmex Corporation fulfilled regulatory requirements and was granted IVD status in Japan for the HISCL  $\beta$ -Amyloid 1-42 and  $\beta$ -Amyloid 1-40 Assay Kits. The kits measure A $\beta$ 42 and A $\beta$ 40 in human plasma and use the A $\beta$ 42/A $\beta$ 40 ratio to detect A $\beta$  pathology in the brain of symptomatic people.<sup>25</sup> The Elecsys<sup>®</sup> Amyloid Plasma Panel (Roche Diagnostics International Ltd) and the PrecivityAD test (C<sub>2</sub>N Diagnostics) have been granted FDA Breakthrough Device Designation,<sup>45,46</sup> which is a program that can accelerate the assay obtaining IVD status by facilitating interactions between assay developers and FDA experts and prioritizing FDA review.<sup>47</sup> The Elecsys Amyloid Plasma Panel combines measurement of phosphorylated tau181 (p-tau181) and apolipoprotein E4 to identify people that would benefit from further confirmatory testing for AD.<sup>45</sup>

**TABLE 1** Differences between selected categories of biomarker tests.

Category	Validated?	Regulatory review/ approval required?	Clinical value	Intended use	Availability
RUO	No clinical validation required	Limited	Gathering real-world evidence on a particular biomarker or disease, supporting product development, and conducting non-clinical laboratory research	Exploratory use only, not to be used for clinical decision making	Widely
LDT	Locally validated	Limited	Reliable test results when performed in the intended laboratory	Limited patient management decisions	At a single laboratory/health-care institution
IVD	Yes, often extensively	Yes <sup>a</sup>	Robust and reliable test results independent of the laboratory in which the test is conducted	Clinical decision making	Widely

Note: Table created using information from references Cummings and Kinney,<sup>18</sup> U.S. Food & Drug Administration,<sup>19</sup> and Teunissen et al.<sup>20</sup>

Abbreviations: IVD, in vitro diagnostic; LDT, laboratory-developed test; RUO, research use only.

<sup>a</sup>In the U.S., IVDs require review by the Food & Drug Administration;<sup>18,21</sup> the European Union has its own Conformité Européenne mark of approval for IVD devices.<sup>22</sup>

Both LDTs and RUOs can be further developed and reclassified as IVDs once extensive analytical and clinical validation have been conducted and regulatory requirements are satisfied.<sup>19,40,48</sup> Analytical validation assesses whether the test is technically robust and will produce reliable and consistent results when conducted in different laboratories under different test conditions. Typical experiments performed during analytical validation include, among others: (1) testing for the degree of agreement between replicate measurements of the same sample under the same conditions (precision), (2) testing for substances affecting the measurable concentration of the analyte sample (interferences),<sup>49</sup> and (3) testing for the ability to obtain results that are proportional to the concentration of analyte being measured (linearity).<sup>50</sup> High robustness indicates that diagnostic performance is unaffected by small differences in test conditions such as pre-analytical sample handling techniques, analytical variability, lab-to-lab, batch-to-batch, and operator differences, all of which are unavoidable in practice.<sup>51</sup> Clinical validation assesses whether the test serves its purpose in the intended use population, that is, whether the test is able to reliably diagnose people with the condition and, in doing so, inform clinical decision making. In real-world terms, a widely validated test with high robustness means that patients are less likely to be misclassified and, hence, are more likely to receive the correct support and treatment. As such, IVDs tend to be one of the most widely used clinical tests<sup>52</sup> and obtaining IVD status is the ultimate goal for many assay developers working in the AD field.

It is worth noting that there are differences in the regulatory approval approaches between the US FDA and the European regulatory bodies. While US approval of a device requires a detailed review process by the FDA, European (Conformité Européenne [CE] mark) registration of some devices can be streamlined to a minimum review/approval effort if the manufacturer's quality management system and the related device group have been previously audited and approved by a European notified body. In addition, the FDA's approach to approving devices is predominantly based on the "predicate device

pathway" or via a comparison with the golden standard, which can make the approval of a new device particularly challenging when it comes to fulfilling regulatory requirements.

### 3 | POTENTIAL CLINICAL VALUE OF PLASMA BIOMARKER TESTING IN THE AD DIAGNOSTIC PATHWAY AND CARE CONTINUUM

Many of the plasma biomarker tests currently available, and in development, for use in the AD field have diagnostic capabilities that would allow them to act as a triage tool to aid in the diagnosis of symptomatic people; however, with ongoing development, plasma biomarker tests have the potential to be used in many different contexts along the AD diagnostic pathway and care continuum (Table 3).

#### 3.1 | Acting as a triage tool by ruling out symptomatic individuals with a low likelihood of A $\beta$ pathology or ruling in symptomatic individuals with a high likelihood of A $\beta$ pathology

In both primary and secondary care settings, plasma biomarker testing could function as a triage tool alongside clinical and neurological investigations to rule out symptomatic individuals with a low likelihood of A $\beta$  pathology or rule in symptomatic individuals with a high likelihood of A $\beta$  pathology. Several of the plasma biomarker tests currently or imminently available are intended to be rule-out triage tools.<sup>35,36</sup> It is suggested that a rule-out test would need to have a negative predictive value (NPV) of > 90% in the intended use population, whereas a rule-in test would need to have a positive predictive value (PPV) of > 90% in the intended use population. A triage tool would assist clinical decision making around whether to: refer the individual for confirmatory PET/CSF biomarker analysis, investigate a different cause of the symptoms, or develop an appropriate plan for treatment and

**TABLE 2** Selected AD plasma biomarker tests that are commercially available or in development.

Test name	Company, location	Measurand(s)	Test category <sup>a</sup>	Regulatory status <sup>a</sup>
<b>Amyloid</b>				
Aβ40 and Aβ42 immunoassays <sup>23,24</sup>	Euroimmun, Lübeck, Germany	Aβ40 and Aβ42	RUO	
HISCL β-Amyloid 1-42 Assay Kit and HISCL β-Amyloid 1-40 Assay Kit <sup>25</sup>	Sysmex Corporation, Kobe, Hyogo, Japan	Aβ40 and Aβ42	IVD	Manufacturing and marketing approval obtained in Japan
Lumipulse G β-Amyloid 1-40 Plasma immunoassay and Lumipulse G β-Amyloid 1-42 Plasma immunoassay <sup>26,27</sup>	Fujirebio, Tokyo, Japan	Aβ40 and Aβ42	RUO	
<b>Tau</b>				
Simoa ptau-181 Advantage V2 Kit <sup>28-30</sup>	Quanterix, Billerica, Massachusetts, USA	p-tau181	RUO	US FDA Breakthrough Device Designation
p-tau181 immunoassay <sup>31</sup>	Washington University, St Louis, Missouri, USA	p-tau181	ND	
p-tau181 immunoassay <sup>28,29,31</sup>	Lilly Research Laboratories, Indianapolis, Indiana, USA	p-tau181	ND	
Simoa p-tau181 immunoassay <sup>28,29,31</sup>	ADx Neurosciences NV, Gent, Belgium	p-tau181	ND	
Simoa p-tau181 immunoassay <sup>28,31</sup>	University of Gothenburg, Sweden	p-tau181	ND	
Lumipulse G pTau 181 immunoassay <sup>31,32</sup>	Fujirebio, Tokyo, Japan	p-tau181	RUO	
S-PLEX p-tau181 kit <sup>31,33</sup>	Meso Scale Discovery, Rockville, Maryland, USA	p-tau181	RUO	
p-tau217 immunoassay <sup>28,29,31</sup>	Lilly Research Laboratories, Indianapolis, Indiana, USA	p-tau217	ND	
Simoa plasma p217+tau assay <sup>28,31</sup>	Janssen Research & Development, LLC, Raritan, New Jersey, USA	p-tau217	ND	
Simoa p-tau231 immunoassay <sup>28,29</sup>	ADx Neurosciences, Gent, Belgium	p-tau231	ND	
Simoa p-tau231 immunoassay <sup>28,29,31</sup>	University of Gothenburg, Sweden	p-tau231	ND	
S-PLEX p-tau231 immunoassay <sup>31,34</sup>	Meso Scale Discovery, Rockville, Maryland, USA	p-tau231	RUO	
t-tau <sup>28</sup>	Lilly Research Laboratories, Indianapolis, Indiana, USA	t-tau	ND	
<b>Panel</b>				
Elecsys® Amyloid Plasma Panel <sup>35</sup>	Roche Diagnostics International Ltd, Rotkreuz, Switzerland	p-tau181, apolipoprotein E4 status	ND	US FDA Breakthrough Device Designation
PrecivityAD <sup>36-38</sup>	C <sub>2</sub> N Diagnostics, St. Louis, Missouri, USA	Aβ42/Aβ40 ratio, apolipoprotein E4 status, age	LDT	US FDA Breakthrough Device Designation
Simoa Neurology 4-Plex E Advantage Kit <sup>23,39</sup>	Quanterix, Billerica, Massachusetts, USA	Aβ40, Aβ42, GFAP, NFL	RUO	

Abbreviations: Aβ, amyloid beta; AD, Alzheimer's disease; FDA, Food & Drug Administration; GFAP, glial fibrillary acidic protein; IVD, in vitro diagnostic; LDT, laboratory-developed test; ND, not disclosed; NFL, neurofilament light chain; p-tau, phosphorylated tau; RUO, research use only; t-tau, total tau.

<sup>a</sup>Test category and status as of April 2023.

support. This could streamline referrals for PET/CSF biomarker analysis and reduce people undergoing unnecessary procedures. In turn, this could improve patient waiting times and help alleviate the burden on specialist physicians, something that would be particularly useful in countries in which patient waiting times are a concern.<sup>53</sup>

A systematic review conducted in the U.S. reported that combining plasma biomarker test results with Mini-Mental State Examination could improve efficiency of identifying patients who are eligible for DMT treatment, while reducing waiting lists and average annual US health-care costs.<sup>54</sup> As DMTs become increasingly available, there will

**TABLE 3** Potential clinical value of plasma biomarkers in the AD diagnostic pathway and care continuum.

Test type	Intended use population clinical description	Intended use population based on clinical stage	Intended use specification	Proposed minimum acceptance criteria <sup>a</sup> , %	Suggested clinical management if positive test result	Suggested clinical management if negative test result
Rule-out test	Individuals with cognitive complaints or impairment	SCD MCI Mild dementia	Triage tool	NPV > 90; PPV > 35	Further assessment needed including PET and/or CSF	Further diagnostic testing required for other causes of cognitive complaints or impairment
Rule-in test	Individuals with cognitive complaints or impairment	SCD MCI Mild dementia	Triage tool	PPV > 90; NPV > 35	A $\beta$ pathology confirmed and PET and/or CSF not required	Confirm negative for A $\beta$ pathology via PET and/or CSF
Enrich clinical trial populations	Individuals with cognitive complaints or impairment	SCD MCI Mild dementia	Pre-trial screening		A $\beta$ pathology confirmed and individual can participate in trial	A $\beta$ pathology not confirmed and individual cannot participate in trial
PET and/or CSF replacement	Individuals with cognitive complaints or impairment	SCD MCI Mild dementia	Confirmatory diagnostic test	PPA > 75 and NPA > 70	A $\beta$ pathology confirmed and individual can be assessed for DMT initiation	A $\beta$ pathology excluded and individual is not eligible for AD-specific DMTs. Further diagnostic testing required for other causes of cognitive complaints or impairment
Predict disease progression	Individuals with MCI or dementia due to AD	Positive for A $\beta$ pathology at confirmatory test	Prognostic test	N.A.	Cognitive symptoms are unlikely to progress	Cognitive symptoms are likely to progress
Monitor treatment response	Individual with confirmed AD taking DMT	Positive for A $\beta$ pathology at confirmatory test	Pharmacodynamic test	N.A.	Treatment is benefiting the individual	Treatment is not benefiting the individual
Monitor treatment safety	Individual with confirmed AD taking DMT	Positive for A $\beta$ pathology at confirmatory test	Safety test	N.A.	Treatment can continue as no safety issues reported	Additional confirmation of adverse event (e.g., MRI to detect ARIA) should be conducted
Screening test for cognitively normal individuals	Asymptomatic individuals	CN	Screening test	NPV > 99	Further assessment by neurologist required	Further referral not required
Screening test for at risk individuals	Asymptomatic individuals at risk of developing AD	CN	Screening test	NPV > 99	Further assessment by neurologist required	Further referral not required

Abbreviations: A $\beta$ , amyloid beta; AD, Alzheimer's disease; ARIA, amyloid-related imaging abnormalities; CN, cognitively normal; CSF, cerebrospinal fluid biomarker analysis; DMT, disease-modifying therapy; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; N.A., not applicable; NPA, negative percentage agreement; NPV, negative predictive value; PET, positron emission tomography; PPA, positive percentage agreement; PPV, positive predictive value; SCD, subjective cognitive decline.

<sup>a</sup>Proposed minimum acceptance criteria are the opinions of the authors. While it is appreciated that NPVs and PPVs are dependent on the prevalence of amyloid positivity in the population in question, any estimate of prevalence is limited by the fact that > 75% of people are undiagnosed globally<sup>3</sup> and up to 30% of people are misdiagnosed.<sup>4</sup>

be a greater need for a triage tool to help identify patients who would benefit from such therapies.

Plasma A $\beta$ 42 concentration and the A $\beta$ 42/A $\beta$ 40 ratio have been widely researched as triage tools, with several tests reporting good diagnostic performances.<sup>39,55</sup> Both the HISCL  $\beta$ -Amyloid 1-42 and  $\beta$ -Amyloid 1-40 Assay Kits (Sysmex Corporation) and the PrecivityAD test (C<sub>2</sub>N Diagnostics) use the A $\beta$ 42/A $\beta$ 40 ratio to identify people with amyloid pathology. In a direct comparison study, the HISCL assays showed high correlation with immunoprecipitation mass spectrometry (Pearson  $r$ : 0.82 and 0.91 for A $\beta$ 42 and A $\beta$ 40, respectively).<sup>56</sup> The PrecivityAD test has also been shown to have good diagnostic performance in retrospective studies using clinical samples;<sup>46,57,58</sup> however, the diagnostic performance of plasma biomarkers may be lower in prospective settings and the test requires mass spectrometry equipment, which may not be easily scalable. Furthermore, the A $\beta$ 42/A $\beta$ 40 ratio has been shown to have an inherently small dynamic range and hence low clinical robustness,<sup>59</sup> meaning that small technical differences when using the tests may result in patients being misclassified.<sup>59</sup> In addition, a 2023 publication found that including age, sex, and/or apolipoprotein E4 carrier status into a risk model did not improve the diagnostic performance compared to the plasma A $\beta$ 42/A $\beta$ 40 ratio alone,<sup>60</sup> a finding that should be considered when assessing the performance of tests that rely on the A $\beta$ 42/A $\beta$ 40 ratio in combination with age, sex, and/or apolipoprotein E4 carrier status.

Plasma p-tau and total tau (t-tau) assays are also under investigation as potential triage tools. Several head-to-head studies have been conducted between a range of plasma p-tau and t-tau assays in a variety of cohorts and settings and report that p-tau181, p-tau217, and p-tau231 are all promising plasma biomarkers for identifying people with A $\beta$  pathology.<sup>28,31,61</sup> A 2021 study reported that plasma p-tau231 levels increased earlier than plasma p-tau181 levels, indicating that plasma p-tau231 may be particularly useful for identifying symptomatic individuals who are early in the AD continuum.<sup>62</sup> Two further studies reported that p-tau231 increases and reaches abnormal levels at lower thresholds of brain amyloidosis than p-tau217 or p-tau181.<sup>63,64</sup>

The Elecsys Amyloid Plasma Panel (Roche Diagnostics International Ltd) is a triage tool that comprises a combination of biomarkers.<sup>35</sup> The Elecsys Amyloid Plasma Panel is based on a retrospective study that assessed a panel of Elecsys prototype immunoassays for clinical performance and robustness in three cohorts. It was found that the p-tau181 and apolipoprotein E4 composite plasma biomarker score was the best-performing combination in terms of meeting the clinical performance and robustness requirements to rule out symptomatic individuals with a low likelihood of A $\beta$  pathology.<sup>51</sup>

### 3.2 | Enriching clinical trial populations by screening out people without A $\beta$ pathology

Several clinical trials are already benefiting from population enrichment using plasma biomarker tests to identify symptomatic individuals with a high likelihood of A $\beta$  pathology, and thereby reducing the number of unnecessary PET and/or CSF biomarker analyses that often take place during pre-trial screening.<sup>12,55</sup> For example, using plasma

p-tau181 and A $\beta$ 42/A $\beta$ 40 measurements to identify suitable trial participants has been found to improve trial screening burden and reduce timelines for participant recruitment.<sup>65</sup>

### 3.3 | Acting as a diagnostic test, replacing confirmatory PET and/or CSF biomarker analysis

Plasma biomarker tests would ideally replace confirmatory PET and/or CSF biomarker analysis in the future for symptomatic individuals, particularly as they are less invasive and easily scalable so are likely to be more accessible.<sup>12,20</sup> Plasma biomarkers could reduce health disparities by improving access, lowering the cost, and eliminating hesitancy around the invasiveness of testing, leading to earlier diagnosis of symptomatic AD, particularly in underserved populations, compared to PET and/or CSF biomarker analysis.<sup>12,66</sup> To replace PET and/or CSF biomarker analysis, a plasma biomarker test would need to be evaluated in prospective multicenter studies and have high diagnostic performance similar to that of PET and/or CSF biomarker analysis. Importantly, the plasma biomarker test would need to provide diagnostic certainty such that a positive result could lead to initiation of DMT treatment. The assays included in Table 2 are not yet able to replace PET and/or CSF biomarker analysis; however, as technology advances and assays become more sensitive and validated in a wide range of populations, it is hoped this will become a reality.

### 3.4 | Predicting disease progression

Plasma biomarker testing may one day be able to predict disease progression in symptomatic individuals. Several studies have examined the relationship between baseline plasma biomarkers and the development of AD. In a study of people without cognitive impairment (CI), people with mild cognitive impairment (MCI) and people with confirmed AD, baseline plasma p-tau181 levels from people with MCI predicted the development of AD 12 months later and were strongly associated with cognitive decline and gray matter loss.<sup>67</sup> A study examining glial fibrillary acidic protein (GFAP) in cognitively normal individuals found that high baseline GFAP levels were associated with an increased risk of developing dementia, thus progressing from asymptomatic to symptomatic disease state.<sup>68</sup> Furthermore, a systematic review concluded that plasma p-tau217 is a sensitive and specific marker for the clinical manifestation of AD and its progression, making it a promising biomarker for predicting disease progression.<sup>69</sup>

### 3.5 | Monitoring disease progression and/or treatment response

Disease progression may be monitored by serial plasma biomarker testing.<sup>12</sup> In a study of people without CI, people with MCI and people with confirmed AD, serial measurements of p-tau181 correlated well with disease progression in all three groups.<sup>70</sup> A further study examining neurofilament light chain (NfL) levels in cognitively normal people



found that NfL rose more steeply in individuals who developed dementia (i.e., progressed from an asymptomatic state to a symptomatic disease state) compared to those who did not.<sup>68</sup> Monitoring plasma biomarker levels could also help physicians identify whether a decline in a patient's condition is due to disease progression, or due to another cause, such as an infection, or an adverse reaction to a new medication.

Plasma biomarker levels are also altered in patients treated with DMTs so could be used to monitor treatment response. A significant decrease in plasma p-tau217 compared to baseline and placebo was observed in patients treated with donanemab.<sup>71</sup> Numerical improvements were also observed for all of the plasma biomarkers examined ( $A\beta_{42}/A\beta_{40}$  ratio, p-tau181, GFAP, and NfL) in patients treated with lecanemab versus placebo in a phase III clinical trial.<sup>14</sup> Similarly, in patients treated with aducanumab, serial reductions in plasma p-tau181 were observed compared to placebo.<sup>13</sup> Plasma biomarker testing is particularly suited to serial monitoring because it is minimally invasive and scalable. It would be useful to guide clinicians about whether a course of treatment is effective and should be continued, or whether it is not slowing disease progression and an alternative treatment should be tried. Furthermore, it would also be of interest to investigate whether there is an association between plasma biomarkers and adverse events due to DMTs to help identify which patients are more likely to experience them.

### 3.6 | Acting as a screening test for cognitively normal individuals or individuals at risk of developing AD

To act as a screening test that can be widely used in primary care, the plasma biomarker test would need to be extremely reliable, with an NPV of >99%, as well as being cost effective.<sup>20</sup> A population screening test of AD is not yet in development, but may be in the future as assays become more accurate and the availability of DMTs increases.<sup>20</sup> With further development, plasma biomarkers may be used as routine screening tools to identify high-risk asymptomatic individuals. They are particularly well suited to screening as they are minimally invasive and scalable. Unlike their applications in symptomatic individuals, such as discriminating AD from other neurological pathologies, the use of plasma biomarker tests in asymptomatic individuals may help to identify high-risk individuals and enable timely implementation of prevention strategies, such as lifestyle interventions, with the potential of delaying and/or preventing cognitive decline. Notably, current FDA-approved DMTs are not indicated for the treatment of asymptomatic individuals.

## 4 | CLINICAL IMPLEMENTATION OF PLASMA BIOMARKER TESTING IN THE AD DIAGNOSTIC PATHWAY AND CARE CONTINUUM

Most plasma biomarker studies have been performed in retrospective studies in well-controlled research-based settings in populations with

low heterogeneity and limited comorbidities.<sup>12</sup> The diagnostic performances of the plasma biomarker tests may therefore be skewed as the intended use population in clinical practice is likely to have lower rates of AD than the participants of a retrospective study. Furthermore, retrospective batch analyses of plasma samples are not affected by between-assay and between-batch variability, which are present in clinical routine use. As such, for a plasma biomarker test to gain IVD status and be deployed globally for routine clinical use, the test must be extensively validated in large, prospective studies in diverse, heterogeneous populations and in settings that accurately reflect real-world clinical practice. Clinical utility will also need to be established; the plasma biomarker test will need to have a positive impact on patient management to secure future reimbursement and wide-scale adoption. In a field-test study conducted in a memory clinic, plasma biomarkers demonstrated excellent diagnostic accuracy compared to current confirmatory diagnostic tests (MRI, PET, and CSF biomarker analysis); it was estimated that plasma biomarker testing reduced the number of confirmatory diagnostic tests needed by up to 49%, highlighting their potential clinical utility as diagnostic tools.<sup>72</sup>

Implementation studies should be undertaken to gather evidence on how plasma biomarker testing can be incorporated in various different clinics and contexts and to examine the most effective ways to use plasma biomarker testing in clinical settings. The expectation is that this will vary depending on the type of clinic and the standard of care within the clinic or geographical region in question but more research is needed. It is likely that a plasma biomarker test will be implemented in secondary care first because test results will need to be interpreted in the context of thorough clinical and neurological examination. At present, the Alzheimer's Association cautiously recommends the use of plasma biomarker tests in specialist memory clinics as part of the diagnostic workup for symptomatic individuals;<sup>73</sup> however, such tests will need to be extensively validated before they can be routinely implemented. For implementation into primary care, training and education of primary care providers would be needed to ensure that tests are conducted in suitable patients and the results are properly interpreted and communicated. Evidence-based appropriate use criteria and clinical implementation guidelines could support this.

From a practical perspective, standardized pre-analytical handling protocols<sup>74,75</sup> and reference standards will be needed to ensure reliable and consistent results are obtained. In addition, further plasma biomarker development that enables researchers to understand and take into consideration co-pathologies, such as Lewy body disease, limbic-predominant age-related TAR DNA-binding protein 43 encephalopathy, or cerebrovascular co-pathology are required. In addition, it has also been shown that chronic kidney disease, hypertension, stroke, and myocardial infarction, which are likely to be prevalent in the intended use population for AD plasma biomarker testing, have an impact on p-tau181 and p-tau217 concentrations, so will need to be considered.<sup>76</sup> Understanding co-pathologies will allow for further patient stratification beyond amyloid and tau proteins to include other proteins that may contribute to cognitive impairment and progression to dementia-like symptoms. The frequency of amyloid deposition and the accumulation of multiple brain pathologies rise with age.

Therefore, in a 50-year-old person, a positive plasma biomarker test would indicate the presence of amyloid pathology that is highly likely to be contributing to their cognitive symptoms, whereas, in a 90-year-old person, a positive plasma biomarker test would still indicate brain amyloidosis, but there may be other pathologies contributing to or causing cognitive symptoms, as cognitive decline and dementia are often due to mixed pathology at that age. More research is needed on how the diagnostic pathway and clinical management may change with age.

## 5 | CONCLUSIONS

Plasma biomarker tests have the potential to revolutionize the AD diagnostic pathway and care continuum and could provide more patients with accurate and timely diagnosis and/or access to treatment, while reducing the burden on health-care facilities. The volume of the scientific literature on plasma biomarkers in AD has increased steeply over the last few years, with almost double the number of publications indexed on PubMed in 2022 as there was in 2019. The purpose of this review was to provide a clinical context for this increasing scientific interest in plasma biomarkers for AD, such that there are important stages of assay development (RUO, LDT, IVD), which are completed to varying degrees and with various regulatory requirements before these plasma biomarker assays are ready for use in clinical routine within the contexts discussed here. Several clinical trials are already using plasma biomarker testing for population enrichment; however, more research and development are needed before patients and health-care facilities will tangibly benefit from plasma biomarker testing in routine use.

### AUTHOR CONTRIBUTIONS

All authors have made a substantial contribution to the conception or design of this manuscript, have reviewed it critically for important intellectual content, have provided final approval of the version to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

### ACKNOWLEDGMENTS

Third-party medical writing assistance, under the direction of the authors, was provided by Anna King, PhD, of Ashfield MedComms (Macclesfield, UK), an Inizio company, and was funded by Roche Diagnostics International Ltd (Rotkreuz, Switzerland). ELECSYS is a trademark of Roche. All other product names and trademarks are the property of their respective owners. This study was funded by Roche Diagnostics International Ltd (Rotkreuz, Switzerland).

### CONFLICT OF INTEREST STATEMENT

Prof. Blennow has served as a paid consultant and attended scientific advisory boards, educational programs, and/or data monitoring committees for Acumen, ALZpath, BioArtic, Biogen, Eisai, Julius Clinical, Lilly, Ono Pharma, Novartis, Roche Diagnostics and

Siemens Healthineers; has received grants to his institution from the Alzheimer's Association (ZEN-21-848495 and SG-23-1038904 QC), Hjärnfonden (Sweden; #FO2017-0243, and #ALZ2022-0006), the Swedish Alzheimer Foundation (#AF-930351, #AF-939721, and #AF-968270), the Swedish Research Council (#2017-00915 and #2022-00732) and the Swedish state (the ALF agreement; #ALFGBG-715986, and #ALFGBG-965240); and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is part of the GU Ventures Incubator Program. Dr. Galasko has served as a paid consultant for Fujirebio and Roche Diagnostics. Prof. Perneczky has received speaker's fees and honoraria from AstraZeneca, Biogen, Eisai, Eli Lilly, Grifols, Janssen-Cilag, Novo Nordisk, Roche, Schwabe, and Tabuk. Prof. Perneczky is supported by the Davos Alzheimer's Collaborative, the Deutsche Forschungsgemeinschaft, the German Center for Neurodegenerative Diseases, the Robert-Vogel-Foundation, the Sheffield National Institute for Health Research Biomedical Research Centre, the University of Cambridge – Ludwig-Maximilians-University Munich Strategic Partnership, and the VERUM Foundation. Dr. Quevenco was previously employed by and owned stock or stock options during employment in Roche Diagnostics International Ltd, Rotkreuz, Switzerland, and Altoida Inc, Washington, DC, USA, and is currently employed by Eli Lilly & Co., Geneva, Switzerland. Dr. Quevenco is also an executive committee member of the Women's Brain Project. Prof. van der Flier runs or has previously run research programs funded by Alzheimer Nederland, AVID, Biogen MA Inc, Combinostics, Edwin Bouw fonds, Eisai, EU-FP7, EU-JPND, Fujifilm, Gieskes-Strijbis fonds, Health~Holland, Hersenstichting CardioVascular Onderzoek Nederland, Life-MI, Novartis-NL, NWO, Pasman stichting, Philips, Roche BV, stichting Alzheimer & Neuropsychiatrie Foundation, stichting Dioraphte, stichting Equilibrio, Topsector Life Sciences & Health, and ZonMW and has been an invited speaker at Biogen MA Inc, Danone, Eisai, European Brain Council (all funding paid to institution), Novo Nordisk, Springer Healthcare, and WebMD Neurology (Medscape). She holds the Pasman chair (Amsterdam University Medical Centre) and has served as a paid consultant for Biogen MA Inc. (all funding paid to institution), Eisai, Oxford Health Policy Forum CIC, and Roche. She has participated on scientific advisory boards for Biogen MA Inc, Roche, and Eli Lilly (all funding paid to institution). She is a member of the steering committee of PAVE and Think Brain Health and was previously an associate editor of *Alzheimer, Research & Therapy* (2020-2021) and is currently an associate editor of *Brain*. Dr. Akinwonmi and Dr. Carboni are currently employed by Roche Diagnostics International Ltd, Rotkreuz, Switzerland and own stock or stock options in F. Hoffmann-La Roche. Dr. Jethwa is currently employed by Roche Diagnostics GmbH, Penzberg, Germany, and is named on a pending European patent application: "A novel antibody for detection of amyloid beta 42 (A $\beta$ 42)". Dr. Suridjan was previously employed by Roche Diagnostics International Ltd, Rotkreuz, Switzerland, and owned stock or stock options in F. Hoffmann-La Roche. Prof. Zetterberg has served as a paid consultant and/or attended scientific advisory boards for AbbVie, Acumen, Alector, Alzinova, ALZPath, Annexon, Apellis, Artery Therapeutics, AZTherapies, CogRx, Denali, Eisai, Nervgen, Novo Nordisk, Optoceutics, Passage Bio, Pinteon Therapeutics, Prothena, Red Abbey Labs, re MYND, Roche, Samumed,

Siemens Healthineers, Triplet Therapeutics, and Wave. He has given lectures in symposia sponsored by Alzecure, Biogen, Cellectric, Fujirebio, and Roche and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is part of the GU Ventures Incubator Program. Prof. Zetterberg is also chair of the Alzheimer's Association Global Biomarker Standardization Consortium and is a Wallenberg Scholar supported by grants from the AD Strategic Fund and the Alzheimer's Association (#ADSF-21-831376-C, #ADSF-21-831381-C, and #ADSF-21-831377-C), the Alzheimer Drug Discovery Foundation USA (#201809-2016862), the Bluefield Project, the European Union Horizon Europe Research and Innovation programme (grant agreement #101053962), the European Union's Horizon 2020 research and innovation program under the Marie Skłodowska-Curie grant (grant agreement #860197; MIRIADE), the European Union Joint Program – Neurodegenerative Disease Research (JPND2021-00694), the Erling-Persson Family Foundation, Hjärfonden (Sweden; #FO2022-0270), the Olav Thon Foundation, the Swedish Research Council (#2022-01018), the Swedish state (the ALF agreement; #ALFGBG-71320), and the UK Dementia Research Institute at UCL (UKDRI-1003). Author disclosures are available in the [supporting information](#).

## REFERENCES

- Alzheimer's Association. 2020 Alzheimer's disease facts and figures. *Alzheimer Dement*. 2020;16(3):391-460. doi:10.1002/alz.12068
- Serrano-Pozo A, Frosch MP, Masliah E, Hyman BT. Neuropathological alterations in Alzheimer disease. *Cold Spring Harb Perspect Med*. 2011;1(1):a006189 doi:10.1101/cshperspect.a006189
- Gauthier S, Webster C, Servaes S, Morais JA, Rosa-Neto P. *Life After Diagnosis: Navigating Treatment, Care and Support*. Alzheimer's Disease International; 2022. Accessed April 2023. <https://www.alzint.org/u/World-Alzheimer-Report-2022.pdf>
- Alzheimer's Association. 2021 Alzheimer's disease facts and figures. *Alzheimer Dement*. 2021;17(3):327-406. doi:10.1002/alz.12328
- Creavin ST, Noel-Storr AH, Langdon RJ, et al. Clinical judgement by primary care physicians for the diagnosis of all-cause dementia or cognitive impairment in symptomatic people. *Cochrane Database Syst Rev*. 2022;6(6):CD012558. doi:10.1002/14651858.CD012558.pub2
- Carboni M, Suridjan I, Yan J, Roth S, Current diagnostic pathways for Alzheimer's disease—a comparison of six countries. Alzheimer's Association International Conference (AAIC); October 9-12, 2022; Bozeman, MT, USA, Poster P-69278.
- National Institute for Health and Care Excellence (NICE). Dementia: assessment, management and support for people living with dementia and their carers. *NICE guideline [NG97]*. National Institute for Health and Care Excellence (NICE); 2018. Accessed April 2023. <https://www.nice.org.uk/guidance/ng97/chapter/Recommendations>
- Anand K, Sabbagh M. Amyloid imaging: poised for integration into medical practice. *Neurotherapeutics*. 2017;14(1):54-61. doi:10.1007/s13311-016-0474-y
- Jie CVML, Treyer V, Schibli R, Mu L. Tauvid™: the first FDA-approved PET tracer for imaging tau pathology in Alzheimer's disease. *Pharmaceuticals (Basel)*. 2021;14(2):110. doi:10.3390/ph14020110
- Roche Diagnostics. Press release: Roche Alzheimer's disease Cerebrospinal Fluid (CSF) assays receive FDA clearance, supporting more accurate and timely diagnosis. 2022. Accessed April 2023. <https://diagnostics.roche.com/us/en/news-listing/2022/roche-alzheimers-disease-cerebrospinal-fluid-assays-receive-fda-clearance.html>
- U.S. Food & Drug Administration (FDA). *Bulletin: FDA Permits Marketing for New Test to Improve Diagnosis of Alzheimer's Disease*. Food and Drug Administration; 2022. Accessed April 2023. <https://content.govdelivery.com/accounts/USFDA/bulletins/3165b47>
- Bittner T. What are the remaining challenges before blood-based biomarkers for Alzheimer's disease can be used in clinical practice? *J Prev Alzheimer's Dis*. 2022;9(4):567-568. doi:10.14283/jpad.2022.89
- Budd Haerberlein S, Aisen PS, Barkhof F, et al. Two randomized phase 3 studies of aducanumab in early Alzheimer's disease. *J Prev Alzheimer's Dis*. 2022;9(2):197-210. doi:10.14283/jpad.2022.30
- van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in early Alzheimer's disease. *N Engl J Med*. 2023;388(1):9-21. doi:10.1056/NEJMoa2212948
- Lilly. Press release: Lilly's donanemab significantly slowed cognitive and functional decline in phase 3 study of early Alzheimer's disease. 2023. Accessed May 2023. <https://investor.lilly.com/news-releases/news-release-details/lillys-donanemab-significantly-slowed-cognitive-and-functional>
- Cummings J, Aisen P, Apostolova LG, Atri A, Salloway S, Weiner M. Aducanumab: appropriate use recommendations. *J Prev Alzheimer's Dis*. 2021;8(4):398-410. doi:10.14283/jpad.2021.41
- Eisai Inc. *US Prescribing Information: LEQEMBI™ (Lecanemab-Irbm) Injection, for Intravenous Use*. January 2023 ed. Eisai R&D Management Co., Ltd; 2023. Accessed April 2023. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2023/761269s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761269s000lbl.pdf)
- Cummings J, Kinney J. Biomarkers for Alzheimer's disease: context of use, qualification, and roadmap for clinical implementation. *Medicina*. 2022;58(7):952. doi:10.3390/medicina58070952
- U.S. Food & Drug Administration (FDA). *Distribution of In Vitro Diagnostic Products Labeled for Research Use Only or Investigational Use Only: Guidance for Industry and Food and Drug Administration Staff*. Food and Drug Administration; 2013. Accessed April 2023. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/distribution-in-vitro-diagnostic-products-labeled-research-use-only-or-investigational-use-only>
- Teunissen CE, Verberk IMW, Thijssen EH, et al. Blood-based biomarkers for Alzheimer's disease: towards clinical implementation. *Lancet Neurol*. 2022;21(1):66-77. doi:10.1016/s1474-4422(21)00361-6
- U.S. Food & Drug Administration (FDA). *Good Clinical Practice (GCP) Requirements for Data Submitted from Clinical Investigations For In Vitro Diagnostic (IVD) Device Premarket Submissions*. Food and Drug Administration; 2021. Accessed April 2023. <https://www.fda.gov/medical-devices/ivd-regulatory-assistance/good-clinical-practice-gcp-requirements-data-submitted-clinical-investigations-in-vitro-diagnostic-ivd>
- Emergo by UL. European CE marking for in vitro diagnostic (IVD) medical devices: experienced technical file preparation and CE marking support for IVD companies. 2022. Accessed April 2023. <https://www.emergobyul.com/services/europe/european-ce-marking-vitro-diagnostic-ivd-medical-devices>
- Janelidze S, Teunissen CE, Zetterberg H, et al. Head-to-head comparison of 8 plasma amyloid- $\beta$  42/40 assays in Alzheimer disease. *JAMA Neurol*. 2021;78(11):1375-1382. doi:10.1001/jamaneurol.2021.3180
- Euroimmun. Plasma beta-amyloid (1-40) ELISA. 2022. Accessed April 2023. <https://www.euroimmun.com/products/antigen-detection/pd/neurodegenerative-diseases/research-parameters/6511/2/138710/>
- Systemex. Press release: Systemex receives manufacturing and marketing approval for an assay kit to identify amyloid beta ( $A\beta$ ) accumulation in the brain, a cause of Alzheimer's disease, using a small amount of blood. 2022. Accessed April 2023. <https://www.systemex.co.jp/en/news/2022/221222.html>
- Fujirebio. Lumipulse® G  $\beta$ -Amyloid 1-40 plasma. 2023. Accessed April 2023. <https://www.fujirebio.com/en/products-solutions/lumipulse-g-beta-amyloid-1-40-plasma>
- Fujirebio. Lumipulse® G  $\beta$ -Amyloid 1-42 plasma. 2023. Accessed April 2023. <https://www.fujirebio.com/en/products-solutions/lumipulse-g-beta-amyloid-1-42-plasma>

28. Ashton NJ, Puig-Pijoan A, Milà-Alomà M, et al. Plasma and CSF biomarkers in a memory clinic: head-to-head comparison of phosphorylated tau immunoassays. *Alzheimer Dement*. 2023;19(5):1913-1924. doi:10.1002/alz.12841
29. Bayoumy S, Verberk IMW, den Dulk B, et al. Clinical and analytical comparison of six simoa assays for plasma p-tau isoforms p-tau181, p-tau217, and p-tau231. *Alzheimers Res Ther*. 2021;13(1):198. doi:10.1186/s13195-021-00939-9
30. Quanterix. Press release: Quanterix granted breakthrough device designation from US FDA for blood-based p tau-181 assay for Alzheimer's disease. 2021. Accessed April 2023. <https://www.quanterix.com/press-releases/quanterix-granted-breakthrough-device-designation-from-u-s-fda-for-blood-based-ptau-181-assay-for-alzheimers-disease/>
31. Janelidze S, Bali D, Ashton NJ, et al. Head-to-head comparison of 10 plasma phospho-tau assays in prodromal Alzheimer's disease. *Brain*. 2023;146(4):1592-1601. doi:10.1093/brain/awac333
32. Fujirebio. Lumipulse® G pTau 181 plasma. 2023. Accessed April 2023. <https://www.fujirebio.com/en/products-solutions/lumipulser-g-ptau-181-plasma>
33. Meso Scale Discovery. S-PLEX Human tau (pT181) kit. Accessed April 2023. <https://www.mesoscale.com/en/products/s-plex-human-tau-pt181-kit-k151agms/>
34. Meso Scale Discovery. S-PLEX human tau (pT231) kit. 2023. Accessed April 2023. <https://www.mesoscale.com/en/products/s-plex-human-tau-pt231-kit-k151agms/>
35. Roche Diagnostics. Press release: Roche's elecsys amyloid plasma panel granted FDA breakthrough device designation to enable a timely diagnosis of Alzheimer's disease. 2022. Accessed April 2023. <https://diagnostics.roche.com/us/en/news-listing/2022/elecsys-amyloid-plasma-panel-fda-breakthrough-device-designation-alzheimers.html>
36. PrecivityAD. Alzheimer's breakthrough: C<sub>2</sub>N first to offer a widely accessible blood test. 2020. Accessed April 2023. <https://precivityad.com/news/alzheimers-breakthrough>
37. Businesswire. C2N diagnostics receives breakthrough device designation from U.S. FDA for blood test to Screen for Alzheimer's disease risk. 2019. Accessed April 2023. <https://www.businesswire.com/news/home/20190129005611/en/C2N-Diagnostics-Receives-Breakthrough-Device-Designation-from-U.S.-FDA-for-Blood-Test-to-Screen-for-Alzheimer%E2%80%99s-Disease-Risk>
38. Galasko DR, Grill JD, Lingler JH, Heidebrink JL. A blood test for Alzheimer's disease: it's about time or not ready for prime time? *J Alzheimers Dis*. 2022;90(3):963-966. doi:10.3233/jad-215490
39. Quanterix. *Simoa Neurology 4-Plex E Advantage Kit HD-X Data Sheet*. Quanterix Corporation; 2018. Accessed April 2023. <https://www.quanterix.com/wp-content/uploads/2020/12/Neurology-4-Plex-E-Data-Sheet-HD-X.pdf>
40. U.S. Food & Drug Administration (FDA). Laboratory developed tests. Silver Spring, MD, USA; Food and Drug Administration. 2018. Accessed April 2023. <https://www.fda.gov/medical-devices/in-vitro-diagnostics/laboratory-developed-tests#:~:text=A%20laboratory%20developed%20test%20>
41. Mertz A. Regulating laboratory-developed tests. *Nat Biotechnol*. 2009;27(5):420-421. doi:10.1038/nbt0509-420
42. Offit K, Sharkey CM, Green D, et al. Regulation of laboratory-developed tests in preventive oncology: emerging needs and opportunities. *J Clin Oncol*. 2023;41(1):11-21. doi:10.1200/jco.22.00995
43. U.S. Food & Drug Administration (FDA). *The Public Health Evidence for FDA Oversight of Laboratory Developed Tests: 20 Case Studies*. Food and Drug Administration; 2015. Accessed April 2023. <https://wayback.archive-it.org/7993/20171114205911/https://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm472773.html>
44. C2N Diagnostics. The PrecivityAD™ test: advanced diagnostics in Alzheimer's disease. 2022. Accessed April 2023. <https://precivityad.com/>
45. Roche Diagnostics. Roche's Elecsys amyloid plasma panel granted FDA breakthrough device designation to enable a timely diagnosis of Alzheimer's disease. 2022. Accessed April 2023. <https://diagnostics.roche.com/us/en/news-listing/2022/elecsys-amyloid-plasma-panel-fda-breakthrough-device-designation-alzheimers.html>
46. Anderson J, Pierce C. PrecivityAD for diagnosis of Alzheimer disease. *Am Fam Physician*. 2022;105(1):79-81.
47. U.S. Food & Drug Administration (FDA). *Breakthrough Devices Program*. Food and Drug Administration; 2023. Accessed April 2023. <https://www.fda.gov/medical-devices/how-study-and-market-your-device/breakthrough-devices-program>
48. Hafen U. The EU regulates medical laboratories – are laboratory developed tests still allowed? 2020. Accessed April 2023. <https://www.johner-institute.com/articles/regulatory-affairs-and-more/the-eu-regulates-medical-laboratories-are-laboratory-developed-tests-still-allowed/>
49. Tate J, Ward G. Interferences in immunoassay. *Clin Biochem Rev*. 2004;25(2):105-120.
50. Andreasson U, Perret-Liaudet A, van Waalwijk van Doorn LJ, et al. A practical guide to immunoassay method validation. *Front Neurol*. 2015;6:179. doi:10.3389/fneur.2015.00179
51. Blennow K, Kurka H, Suridjan I, et al. P-69052: clinical performance and robustness of blood-based biomarkers for early detection of amyloid pathology associated with Alzheimer's disease. Alzheimer's Association International Conference (AAIC); 31 July–4 August 2022; San Diego, CA, USA. Poster.
52. The PEW Charitable Trusts. What are in vitro diagnostic tests, and how are they regulated? Oversight may not be keeping pace with changes in the diagnostics market. Accessed April 2023. 2019. <https://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2019/05/what-are-in-vitro-diagnostic-tests-and-how-are-they-regulated>
53. Mattke S, Hanson M. Expected wait times for access to a disease-modifying Alzheimer's treatment in the United States. *Alzheimers Dement*. 2022;18(5):1071-1074. doi:10.1002/alz.12470
54. Mattke S, Cho SK, Bittner T, Hlávka J, Hanson M. Blood-based biomarkers for Alzheimer's pathology and the diagnostic process for a disease-modifying treatment: projecting the impact on the cost and wait times. *Alzheimers Dement*. 2020;12(1):e12081. doi:10.1002/dad2.12081
55. Leuzy A, Mattsson-Carlgrén N, Palmqvist S, Janelidze S, Dage JL, Hansson O. Blood-based biomarkers for Alzheimer's disease. *EMBO Mol Med*. 2022;14(1):e14408. doi:10.15252/emmm.202114408
56. Yamashita K, Watanabe S, Ishiki K, et al. Fully automated chemiluminescence enzyme immunoassays showing high correlation with immunoprecipitation mass spectrometry assays for  $\beta$ -amyloid (1-40) and (1-42) in plasma samples. *Biochem Biophys Res Commun*. 2021;576:22-26. doi:10.1016/j.bbrc.2021.08.066
57. Kirmess KM, Meyer MR, Holubasch MS, et al. The PrecivityAD™ test: accurate and reliable LC-MS/MS assays for quantifying plasma amyloid beta 40 and 42 and apolipoprotein E proteotype for the assessment of brain amyloidosis. *Clin Chim Acta*. 2021;519:267-275. doi:10.1016/j.cca.2021.05.011
58. West T, Kirmess KM, Meyer MR, et al. A blood-based diagnostic test incorporating plasma A $\beta$ 42/40 ratio, ApoE proteotype, and age accurately identifies brain amyloid status: findings from a multi cohort validity analysis. *Mol Neurodegener*. 2021;16(1):30. doi:10.1186/s13024-021-00451-6

59. Rab C, Bittner T, Jethwa A, et al. Clinical performance and robustness evaluation of plasma amyloid- $\beta_{42/40}$  prescreening. *Alzheimers Dement*. 2023;19:1393-1402. doi:10.1002/alz.12801
60. Winston CN, Langford O, Levin N, et al. Evaluation of blood-based plasma biomarkers as potential markers of amyloid burden in preclinical Alzheimer's disease. *J Alzheimers Dis*. 2023;92(1):95-107. doi:10.3233/jad-221118
61. Suárez-Calvet M, Ashton NJ, Puig-Pi Joan A, et al. A head-to-head comparison of plasma phosphorylated tau assays in the real-world memory clinic. *Alzheimer Dement*. 2022;18(S6):e065391. doi:10.1002/alz.065391
62. Ashton NJ, Pascoal TA, Karikari TK, et al. Plasma p-tau231: a new biomarker for incipient Alzheimer's disease pathology. *Acta Neuropathol*. 2021;141(5):709-724. doi:10.1007/s00401-021-02275-6
63. Milà-Alomà M, Ashton NJ, Shekari M, et al. Publisher Correction: plasma p-tau231 and p-tau217 as state markers of amyloid- $\beta$  pathology in preclinical Alzheimer's disease. *Nat Med*. 2022;28(9):1965. doi:10.1038/s41591-022-02037-1
64. Ashton NJ, Janelidze S, Mattsson-Carlsson N, et al. Differential roles of A $\beta_{42/40}$ , p-tau231 and p-tau217 for Alzheimer's trial selection and disease monitoring. *Nat Med*. 2022;28(12):2555-2562. doi:10.1038/s41591-022-02074-w
65. Rissman RA, Langford O, Donohue M, et al. Plasma levels of ABeta42/40 and P-tau217 ratios increase accuracy of amyloid PET prediction in preclinical AD. *J Prev Alzheimer Dis*. 2022;9(suppl 1):S40-S41. Abstract LB42. Accessed April 2023. <https://www.ctad-alzheimer.com/files/files/JPAD%20CTAD%20abstracts.pdf>
66. Lang L, Clifford A, Wei L, et al. Prevalence and determinants of undetected dementia in the community: a systematic literature review and a meta-analysis. *BMJ Open*. 2017;7(2):e011146. doi:10.1136/bmjopen-2016-011146
67. Simrén J, Leuzy A, Karikari TK, et al. The diagnostic and prognostic capabilities of plasma biomarkers in Alzheimer's disease. *Alzheimer Dement*. 2021;17(7):1145-1156. doi:10.1002/alz.12283
68. Verberk IMW, Laarhuis MB, van den Bosch KA, et al. Serum markers glial fibrillary acidic protein and neurofilament light for prognosis and monitoring in cognitively normal older people: a prospective memory clinic-based cohort study. *Lancet Healthy Longev*. 2021;2(2):e87-e95. doi:10.1016/s2666-7568(20)30061-1
69. Telsler J, Risch L, Saely CH, Grossmann K, Werner P. P-tau217 in Alzheimer's disease. *Clin Chim Acta*. 2022;531:100-111. doi:10.1016/j.cca.2022.03.018
70. Chen SD, Huang YY, Shen XN, et al. Longitudinal plasma phosphorylated tau 181 tracks disease progression in Alzheimer's disease. *Transl Psychiatry*. 2021;11(1):356. doi:10.1038/s41398-021-01476-7
71. Sims JR, Lu M, Schade AE, Brooks DA, Mintun MA. TRAILBLAZER-ALZ: three clinical trials of Donanemab in early Alzheimer's disease. *J Prev Alzheimers Dis*. 2021;8(suppl 1):S2-S4. Oral Presentations 1-3. Accessed April 2023. [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8589633/pdf/42414\\_2021\\_Article\\_146.pdf](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8589633/pdf/42414_2021_Article_146.pdf)
72. Altomare D, Stampacchia S, Ribaldi F, et al. Plasma biomarkers for Alzheimer's disease: a field-test in a memory clinic. *J Neurol Neurosurg Psychiatry*. 2023;94(6):420-427. doi:10.1136/jnnp-2022-330619
73. Hansson O, Edelmayer RM, Boxer AL, et al. The Alzheimer's Association appropriate use recommendations for blood biomarkers in Alzheimer's disease. *Alzheimers Dement*. 2022;18(12):2669-2686. doi:10.1002/alz.12756
74. Verberk IMW, Misdorp EO, Koelewijn J, et al. Characterization of pre-analytical sample handling effects on a panel of Alzheimer's disease-related blood-based biomarkers: results from the Standardization of Alzheimer's Blood Biomarkers (SABB) working group. *Alzheimers Dement*. 2022;18(8):1484-1497. doi:10.1002/alz.12510
75. Kurz C, Stöckl L, Schürs I, et al. Impact of pre-analytical sample handling factors on plasma biomarkers of Alzheimer's disease. *J Neurochem*. 2023;165:95-105. doi:10.1111/jnc.15757
76. Mielke MM, Dage JL, Frank RD, et al. Performance of plasma phosphorylated tau 181 and 217 in the community. *Nat Med*. 2022;28(7):1398-1405. doi:10.1038/s41591-022-01822-2

#### SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Blennow K, Galasko D, Perneczky R, et al. The potential clinical value of plasma biomarkers in Alzheimer's disease. *Alzheimer's Dement*. 2023;1-12. <https://doi.org/10.1002/alz.13455>