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REVIEW ARTICLE

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

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

[1]Institute of Neuroscience and Physiology, Department of Psychiatry and Neurochemistry, Sahlgrenska Academy, University of Gothenburg, Mölndal, Sweden

[2]Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden

[3]Department of Neurosciences, University of California, San Diego, La Jolla, California, USA

[4]Department of Psychiatry and Psychotherapy, University Hospital of Munich, Munich, Germany

[5]German Center for Neurodegenerative Diseases (DZNE), Munich, Germany

[6]Munich Cluster for Systems Neurology (SyNergy), Munich, Germany

[7]Sheffield Institute for Translational Neuroscience (SITraN), University of Sheffield, Broomhall, Sheffield, UK

[8]Ageing Epidemiology (AGE) Research Unit, School of Public Health, Imperial College London, London, UK

[9]Roche Diagnostics International Ltd, Rotkreuz, Switzerland

[10]Department of Neurology, Alzheimer Centre Amsterdam, Amsterdam UMC, Amsterdam, The Netherlands

[11]Amsterdam Neuroscience, Neurodegeneration, Amsterdam UMC, Amsterdam, The Netherlands

[12]Department of Epidemiology and Data Science, Amsterdam UMC, Amsterdam, The Netherlands

[13]Roche Diagnostics GmbH, Penzberg, Germany

[14]UK Dementia Research Institute, UCL, London, UK

[15]Department of Neurodegenerative Disease, UCL Institute of Neurology, London, UK

[16]Hong Kong Center for Neurodegenerative Diseases, Hong Kong Special Administrative Region, Hong Kong, China

[17]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

[†]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.

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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 ≈ 60% to 80% of dementia cases.[1] It is characterized by abnormal amyloid beta (Aβ) deposition in the form of amyloid plaques (Aβ pathology), as well as neurofibrillary tangles, dystrophic neurites and neuropil threads composed of hyperphosphorylated tau proteins (tau pathology) in the brain.[2] Alzheimer's Disease International estimate that, on average, > 75% of people living with cognitive complaints or impairment are undiagnosed worldwide[3] and *post mortem* studies report misdiagnosis rates of up to 30%.[4] 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.[5]

Globally, there is no standardized AD diagnostic pathway.[6] 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.[7] Diagnosis of AD can be supported by positron emission tomography (PET) and/or cerebrospinal fluid (CSF) biomarker analysis,[7] both of which are approved by the U.S. Food & Drug Administration (FDA) for the diagnosis of AD.[8–11] However, use of these confirmatory tests is limited due to perceived invasiveness, high costs, and lack of specialist equipment and/or clinical expertise.[12]

Certifying the presence of Aβ pathology in the brain in vivo is important for clinical decision making, particularly with the advancement of anti-Aβ disease-modifying therapies (DMTs), such as aducanumab[13] and lecanemab,[14] which are FDA approved, and donanemab,[15] 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;[13–15] 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.[16,17] 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).[18] 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.

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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 Aβ pathology or ruling in symptomatic individuals with a high likelihood of Aβ pathology
- Enriching clinical trial populations by screening out people without Aβ 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.[19] 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."[18,19]

LDTs are designed, manufactured, and used in a single laboratory or laboratory network[18,40] 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.[40,41] They can also be modified to allow for the rapid incorporation of new findings.[41] 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.[42] 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.[43] The PrecivityAD test (C_2N Diagnostics) is an LDT that assesses the likelihood that a person has Aβ pathology by quantitatively measuring the plasma Aβ42/Aβ40 ratio and combining this measurement with apolipoprotein E4 status and age to provide an AD risk score.[44] 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.[27,38]

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.[18,22,20] In December 2022, Sysmex Corporation fulfilled regulatory requirements and was granted IVD status in Japan for the HISCL β-Amyloid 1-42 and β-Amyloid 1-40 Assay Kits. The kits measure Aβ42 and Aβ40 in human plasma and use the Aβ42/Aβ40 ratio to detect Aβ pathology in the brain of symptomatic people.[25] The Elecsys® Amyloid Plasma Panel (Roche Diagnostics International Ltd) and the PrecivityAD test (C_2N Diagnostics) have been granted FDA Breakthrough Device Designation,[45,46] 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.[47] 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.[45]

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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[a]	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,[18] U.S. Food & Drug Administration,[19] and Teunissen et al.[20]
Abbreviations: IVD, in vitro diagnostic; LDT, laboratory-developed test; RUO, research use only.
[a]In the U.S., IVDs require review by the Food & Drug Administration;[18,21] the European Union has its own Conformitè Europëenne mark of approval for IVD devices.[22]

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.[19,40,48] 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),[49] and (3) testing for the ability to obtain results that are proportional to the concentration of analyte being measured (linearity).[50] 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.[51] 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[52] 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 Aβ pathology or ruling in symptomatic individuals with a high likelihood of Aβ 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 Aβ pathology or rule in symptomatic individuals with a high likelihood of Aβ pathology. Several of the plasma biomarker tests currently or imminently available are intended to be rule-out triage tools.[35,36] 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

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

Test name	Company, location	Measurand(s)	Test category[a]	Regulatory status[a]
Amyloid				
Aβ40 and Aβ42 immunoassays[23,24]	Euroimmun, Lübeck, Germany	Aβ40 and Aβ42	RUO	
HISCL β-Amyloid 1-42 Assay Kit and HISCL β-Amyloid 1-40 Assay Kit[25]	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[26,27]	Fujirebio, Tokyo, Japan	Aβ40 and Aβ42	RUO	
Tau				
Simoa ptau-181 Advantage V2 Kit[28–30]	Quanterix, Billerica, Massachusetts, USA	p-tau181	RUO	US FDA Breakthrough Device Designation
p-tau181 immunoassay[31]	Washington University, St Louis, Missouri, USA	p-tau181	ND	
p-tau181 immunoassay[28,29,31]	Lilly Research Laboratories, Indianapolis, Indiana, USA	p-tau181	ND	
Simoa p-tau181 immunoassay[28,29,31]	ADx Neurosciences NV, Gent, Belgium	p-tau181	ND	
Simoa p-tau181 immunoassay[28,31]	University of Gothenburg, Sweden	p-tau181	ND	
Lumipulse G pTau 181 immunoassay[31,32]	Fujirebio, Tokyo, Japan	p-tau181	RUO	
S-PLEX p-tau181 kit[31,33]	Meso Scale Discovery, Rockville, Maryland, USA	p-tau181	RUO	
p-tau217 immunoassay[28,29,31]	Lilly Research Laboratories, Indianapolis, Indiana, USA	p-tau217	ND	
Simoa plasma p217+tau assay[28,31]	Janssen Research & Development, LLC, Raritan, New Jersey, USA	p-tau217	ND	
Simoa p-tau231 immunoassay[28,29]	ADx Neurosciences, Gent, Belgium	p-tau231	ND	
Simoa p-tau231 immunoassay[28,29,31]	University of Gothenburg, Sweden	p-tau231	ND	
S-PLEX p-tau231 immunoassay[31,34]	Meso Scale Discovery, Rockville, Maryland, USA	p-tau231	RUO	
t-tau[28]	Lilly Research Laboratories, Indianapolis, Indiana, USA	t-tau	ND	
Panel				
Elecsys® Amyloid Plasma Panel[35]	Roche Diagnostics International Ltd, Rotkreuz, Switzerland	p-tau181, apolipoprotein E4 status	ND	US FDA Breakthrough Device Designation
PrecivityAD[36–38]	C_2N 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[23,39]	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.
[a]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.[53]

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.[54] As DMTs become increasingly available, there will

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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[a], %	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	Aβ pathology confirmed and PET and/or CSF not required	Confirm negative for Aβ pathology via PET and/or CSF
Enrich clinical trial populations	Individuals with cognitive complaints or impairment	SCD MCI Mild dementia	Pre-trial screening		Aβ pathology confirmed and individual can participate in trial	Aβ 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	Aβ pathology confirmed and individual can be assessed for DMT initiation	Aβ 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 Aβ 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 Aβ pathology at confirmatory test	Pharmaco-dynamic 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 Aβ 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: Aβ, 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.

[a] 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[3] and up to 30% of people are misdiagnosed.[4]

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

Plasma Aβ42 concentration and the Aβ42/Aβ40 ratio have been widely researched as triage tools, with several tests reporting good diagnostic performances.[39,55] Both the HISCL β-Amyloid 1-42 and β-Amyloid 1-40 Assay Kits (Sysmex Corporation) and the PrecivityAD test (C_2N Diagnostics) use the Aβ42/Aβ40 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 Aβ42 and Aβ40, respectively).[56] The PrecivityAD test has also been shown to have good diagnostic performance in retrospective studies using clinical samples;[46,57,58] 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 Aβ42/Aβ40 ratio has been shown to have an inherently small dynamic range and hence low clinical robustness,[59] meaning that small technical differences when using the tests may result in patients being misclassified.[59] 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 Aβ42/Aβ40 ratio alone,[60] a finding that should be considered when assessing the performance of tests that rely on the Aβ42/Aβ40 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 Aβ pathology.[28,31,61] 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.[62] Two further studies reported that p-tau231 increases and reaches abnormal levels at lower thresholds of brain amyloidosis than p-tau217 or p-tau181.[63,64]

The Elecsys Amyloid Plasma Panel (Roche Diagnostics International Ltd) is a triage tool that comprises a combination of biomarkers.[35] 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 Aβ pathology.[51]

3.2 | Enriching clinical trial populations by screening out people without Aβ pathology

Several clinical trials are already benefiting from population enrichment using plasma biomarker tests to identify symptomatic individuals with a high likelihood of Aβ pathology, and thereby reducing the number of unnecessary PET and/or CSF biomarker analyses that often take place during pre-trial screening.[12,55] For example, using plasma p-tau181 and Aβ42/Aβ40 measurements to identify suitable trial participants has been found to improve trial screening burden and reduce timelines for participant recruitment.[65]

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.[12,20] 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.[12,66] 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.[67] 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.[68] 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.[69]

3.5 | Monitoring disease progression and/or treatment response

Disease progression may be monitored by serial plasma biomarker testing.[12] 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.[70] A further study examining neurofilament light chain (NfL) levels in cognitively normal people

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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.[68] 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.[71] Numerical improvements were also observed for all of the plasma biomarkers examined (Aβ42/Aβ40 ratio, p-tau181, GFAP, and NfL) in patients treated with lecanemab versus placebo in a phase III clinical trial.[14] Similarly, in patients treated with aducanumab, serial reductions in plasma p-tau181 were observed compared to placebo.[13] 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.[20] 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.[20] 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.[12] 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, heterogenous 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.[72]

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;[73] 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[74,75] 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.[76] 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.

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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.

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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 (Aβ42)". 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,

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Siemens Healthineers, Triplet Therapeutics, and Wave. He has given lectures in symposia sponsored by Alzecure, Biogen, Cellectricon, 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, Hjärnfonden (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.

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SUPPORTING INFORMATION

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

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