Short communication

Journal of Alzheimer's Disease Reports
Volume 10: 1–6

DOI: 10.1177/25424823261437790
journals.sagepub.com/home/alr

Perspectives on plasma biomarkers for point-of-care diagnostics in Alzheimer's disease: Insights into 2D-BioPAD

Angeliki Koukoura[1], Kyriaki Antonopoulou[1], Apostolos C Tsolakis[2], Alina Solomon[3], Magda Tsolaki[4], Lutz Froelich[5], Anthoula Tsolaki[4], Eirini Papadaki[1], Efstathios Vassiliadis[1] and Gitte Juel Holst[1]

Abstract

We investigated the potential of plasma biomarkers for point-of-care in vitro diagnostics in Alzheimer's disease by collecting insights from 99 stakeholders primarily from Greece, including patients, caregivers, healthcare professionals, and researchers. Data from an online survey was analyzed using descriptive statistics and thematic analysis. Key biomarkers reported by participants included $A\beta_{40}$, $A\beta_{42}$, pTau181, pTau217, and neurofilament light chain. While biomarkers were recognized for their value in prognosis, diagnosis, and monitoring, most participants were unfamiliar with point-of-care in vitro diagnostics. Major concerns regarding implementation included cost, reimbursement, and accessibility, underscoring the need for more feasible and context-appropriate diagnostic solutions.

Keywords

Alzheimer's disease, biomarkers, dementia, health care professionals, in vitro diagnostic devices, patient engagement, patient involvement

Received: 30 October 2025; accepted: 13 March 2026

Introduction

Current diagnostic techniques for Alzheimer's disease (AD), such as magnetic resonance imaging (MRI), positron emission tomography (PET) scans (amyloid, tau, fluorodeoxyglucose (FDG)), lumbar puncture for cerebrospinal fluid (CSF) biomarkers, and neuropsychological assessments, are well-established but often costly, invasive, procedurally complex, limited in accessibility and typically confirm AD only after clinical symptoms have emerged. Since 2018, validated biomarkers including amyloid-β and tau PET, CSF $A\beta_{42}$, $A\beta_{42}/A\beta_{40}$ ratio, total tau (t-tau), and phosphorylated tau (pTau181) have entered clinical practice.[1–3]

Blood-based biomarkers (BBMs) represent a promising complementary diagnostic tool, offering greater accessibility, cost-effectiveness, and minimal invasiveness. BBMs can aid in identifying asymptomatic individuals and guiding early interventions, as proteins derived from brain pathology can be detected in peripheral blood and reflect underlying AD processes.[4] BBMs associated with abnormal protein accumulation, such as amyloid-beta and tau, correlate with PET imaging, CSF biomarkers, and cognitive stages, with measures like the $A\beta_{42/40}$ ratio demonstrating high diagnostic accuracy for detecting brain amyloid-beta burden.[4,5] Although BBMs alone are insufficient for a definitive diagnosis, they may significantly enhance early detection when used alongside clinical evaluation.[6] Recent research has focused on refining BBMs for use in

[1]Evnia ApS, INCUBA NAVITAS, Aarhus C, Denmark
[2]Q-PLAN International Advisors PC, Thessaloniki, Greece
[3]Department of Neurology, Institute of Clinical Medicine, University of Eastern Finland, Kuopio, Finland
[4]Greek Association of Alzheimer's Disease and Related Disorders, Thessaloniki, Greece
[5]Department Geriatric Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany

Corresponding author:
Angeliki Koukoura, Evnia ApS, Inge Lehmanns Gade 10, INCUBA NAVITAS, 8000 Aarhus C, Denmark.
Email: anko@evnia.dk

Table 1. Online survey demographic characteristics.

Demographic Characteristics by participant profile												
Online Survey Group												
	Patients (N=12)		Caregivers (N=31)		Decision Makers (N=14)		HCPs Primary (N=8)		HCPs Specialized (N=21)		Biomarker Experts (N=13)	
	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage
Main Country of Residence												
Czech Republic	1	8.33%	0	0%	0	0%	0	0%	0	0%	0	0%
Denmark	0	0%	0	0%	1	7.14%	0	0%	0	0%	0	0%
Finland	1	8.33%	0	0%	0	0%	0	0%	3	14.29%	0	0%
France	0	0%	0	0%	0	0%	0	0%	0	0%	2	15.38%
Germany	0	0%	1	3.23%	2	14.29%	0	0%	4	19.05%	1	7.69%
Greece	10	83.33%	28	90.32%	9	64.29%	8	100%	14	66.67%	2	15.38%
Ireland	0	0%	1	3.23%	1	7.14%	0	0%	0	0%	0	0%
Spain	0	0%	0	0%	0	0%	0	0%	0	0%	4	30.77%
Other	0	0%	1	3.23%	1	7.14%	0	0%	0	0%	4	30.77%
Education Level												
Primary education	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
High-school degree	1	8.33%	1	3.23%	0	0%	0	0%	0	0%	0	0%
Occupationally specific program	2	16.67%	1	3.23%	1	7.14%	0	0%	0	0%	0	0%
Bachelor's degree	6	50%	12	38.71%	2	14.29%	0	0%	0	0%	1	7.69%
Master's degree	1	8.33%	9	29.03%	3	21.43%	3	37.50%	7	33.33%	2	15.38%
Philosophy Doctorate (PhD)	2	16.67%	4	12.9%	3	21.43%	1	12.50%	0	0%	2	15.38%
Post Doctoral (Post-Doc)	0	0%	2	6.45%	1	7.14%	0	0%	1	4.76%	8	61.54%
Medical degree	0	0%	1	3.23%	2	14.29%	3	37.50%	9	42.86%	0	0%
Internship	0	0%	1	3.23%	2	14.29%	0	0%	3	14.29%	0	0%
Residency	0	0%	0	0%	1	7.14%	1	12.50%	1	4.76%	0	0%
Level of experience in AD Biomarkers												
None	8	66.67%	24	77.42%	2	14.29%	2	25%	7	33.33%	1	7.69%
Novice	2	16.67%	5	16.13%	3	21.43%	2	25%	6	28.57%	2	15.38%
Advanced beginner	2	16.67%	1	3.23%	2	14.29%	3	37.5%	3	14.29%	1	7.69%
Competent	0	0%	1	3.23%	3	21.43%	0	0%	2	9.52%	6	46.15%
Proficient	0	0%	0	0%	4	28.57%	1	12.5%	2	9.52%	1	7.69%
Expert	0	0%	0	0%	0	0%	0%	0%	1	4.76%	2	15.38%
Level of experience in PoC IVD												
None	10	83.33%	25	80.65%	6	42.86%	3	37.5%	14	66.67%	1	7.69%
Novice	0	0%	5	16.13%	4	28.57%	3	37.5%	4	19.05%	5	38.46%
Advanced beginner	2	16.67%	0	0%	1	7.14%	0	0%	0	0%	1	7.69%
Competent	0	0%	1	3.23%	1	7.14%	0	0%	2	9.52%	2	15.38%
Proficient	0	0%	0	0%	2	14.29%	2	25%	1	4.76%	1	7.69%
Expert	0	0%	0	0%	0	0	0	0%	0	0%	3	23.08%

primary care and point-of-care (PoC) diagnostics, aiming to improve accessibility and reduce diagnostic delays.[7,8]

This study aimed to explore the perspectives of diverse stakeholders, including patients, caregivers, healthcare professionals (HCPs), decision-makers, and AD biomarker researchers, on the potential role of BBMs in PoC in vitro diagnostic (IVD) systems. The goal was to assess awareness, perceived value, and barriers to adoption across the AD continuum, and to inform the design of a PoC IVD device under development by the 2D-BioPAD consortium funded by the European Union (GA no. 101120706).

Methods

The 2D-BioPAD project included an online survey to gather insights from six stakeholder groups (Table 1).[9] These comprised patients, to assess awareness and attitudes toward AD; caregivers, to understand challenges in care provision; HCPs from both primary and specialized care, to gather diagnostic and management perspectives; biomarker experts, to identify gaps in biomarker development; and decision-makers, to explore policy considerations at national and European levels.

The survey was designed to collect broad, high-level insights from a European audience regarding their needs, concerns, and potential barriers to the acceptance of AD diagnostics. Participation was voluntary, and anonymity and confidentiality were ensured through a public registration method. The survey was promoted via the 2D-BioPAD consortium's social media platforms and distributed through clinical centers and AD-related networks.[10]

A total of 99 participants (Table 1) were enrolled in the study from 15/02/2024 to 06/03/2024. This included 12 patients and 31 caregivers from AD association centers in Greece and Finland, 14 decision-makers, 29 healthcare professionals, of whom 8 were from primary care and 21 from specialized care, and 13 biomarker experts. Data were analyzed using STATA 17.0 SE. Prior to formal analysis, several data cleaning steps were undertaken. These included the removal of incomplete or erroneous responses, translation of non-English characters such as Greek symbols from open-ended answers, identification and resolution of outliers, and recoding or categorization of variables to ensure consistency and accuracy.

Descriptive statistics were used to summarize categorical variables, which were reported as frequencies and percentages. Continuous variables were presented as medians and IQR. For multiple-response questions, each response option was treated as a separate dichotomous variable (selected vs. not selected). Results were reported using both the percentage of responses (based on total selections) and the percentage of cases (based on total respondents).

Results

Experience with PoC IVD applications and AD biomarkers was generally low across all stakeholder groups: 59.6% of participants reported no prior experience with PoC IVDs, and 44.4% reported no experience with AD biomarkers (Table 1). Several biomarkers were consistently reported across professional groups as important for prognosis, early diagnosis, and disease monitoring. These included $A\beta_{40}$, $A\beta_{42}$, the $A\beta_{42}/A\beta_{40}$ ratio, tau proteins (pTau181, pTau217, pTau231), and neurofilament light chain (NfL). Biomarkers that consistently received high scores across all categories—prognosis, diagnosis, and progression monitoring—were the $A\beta_{42}/A\beta_{40}$ ratio and tau protein 181. Moreover, healthcare professionals were generally less aware of glial fibrillary acidic protein (GFAP) and TAR DNA-binding protein (TDP-43) compared to biomarker experts (Table 2).

Participants also identified several key challenges to the implementation of BBMs and PoC diagnostics. The most frequently cited barriers were knowledge gaps among

Table 2. Biomarker ratings.

	Prognosis (Median) (IQR)		Early diagnosis (Median) (IQR)		Progression Monitoring (Median) (IQR)	
Biomarkers	Biomarker Experts (N=12)	HCPs (N=14)	Biomarker Experts (N=12)	HCPs (N=14)	Biomarker Experts (N=12)	HCPs (N=14)
Amyloid Beta (Aβ) 1–40	3.5 (2–4)	3 (1–4)	3 (1.5–4.5)	3.5 (1–4)	3.5 (2–4)	3 (0–4)
Amyloid Beta (Aβ) 1–42	4 (4–4)	3.5 (3–4)	4 (3.5–4)	4 (3–4)	4 (2–4)	3.5 (3–4)
Aβ42/Aβ40 ratio	4 (3.5–4)	4 (3–5)	4 (3.5–4)	4 (4–5)	4 (3–4)	4 (3–4)
Tau Protein 181	4 (3.5–4)	3.5 (0–4)	4 (4–4)	4 (2–4)	4 (3–4)	4 (1–4)
Tau Protein 217	4 (3.5–4)	3.5 (0–4)	4 (3.5–4)	3.5 (0–4)	4 (4–4)	3.5 (0–4)
Tau Protein 231	4 (2.5–4)	1.5 (0–4)	4 (2.5–4)	1.5 (0–4)	4 (3–4)	1.5 (0–4)
Neurofilament Light chain (NfL)	3.5 (0.5–4)	3 (0–4)	3.5 (0.5–4)	3 (0–4)	3.5 (0.5–4)	3 (0–4)
Glial Fibrillary Acidic Protein	3.5 (0–4)	0 (0–4)	4 (0–4)	0.5 (0–4)	3 (0–4)	0 (0–4)
TDP-43	3 (0–3.5)	0 (0–3)	3.5 (0–4)	0 (0–4)	3 (0–4)	0 (0–3)

Note: In the Online Survey a 5-point rating scale was used, from 0 ("No Opinion") to 5 ("Very Important").

Table 3. Key challenges to implementing PoC IVDs for plasma-based AD biomarkers in primary care.

Which are the main challenges and/or barriers to deploying a PoC IVD for detecting AD blood-derived (plasma) biomarkers in primary healthcare settings?	HCPs Specialized			HCPs Primary			Biomarker Experts			Decision Makers		
	N	Percentage of responses	Percentage of cases	N	Percentage of responses	Percentage of cases	N	Percentage of responses	Percentage of cases	N	Percentage of responses	Percentage of cases
Lack of awareness from patients	8	13.79%	44.44%	1	4%	12.5%	5	10.2%	41.67%	5	12.5%	38.46%
Lack of knowledge/expertise from HCPs	8	13.79%	44.44%	4	16%	50%	6	12.24%	50%	10	25%	76.92%
High Testing Cost (Pricing/Cost)	10	17.24%	55.56%	4	16%	50%	6	12.24%	50%	6	15%	46.15%
Unreliable performance over time and clinical use (Robustness/Reliability)	4	6.9%	22.22%	1	4%	12.5%	6	12.24%	50%	3	7.5%	23.08%
Non-credible results/lack of trustworthy outcomes (Credibility/ Trustworthiness)	7	12.07%	38.89%	3	12%	37.5%	4	8.16%	33.33%	3	7.5%	23.08%
Difficult or complex to use – overhead for already overburdened personnel (Complexity/User-friendliness)	3	5.17%	16.67%	2	8%	25%	4	8.16%	33.33%	1	2.5%	7.69%
Not covered by existing insurance programs – costs will be covered by the patient (Reimbursement/Health Insurance coverage)	8	13.79%	44.44%	5	20%	62.5%	5	10.2%	41.67%	5	12.5%	38.46%
Not compatible with existing clinical information systems (interoperability)	3	5.17%	16.67%	0	0%	0%	4	8.16%	33.33%	3	7.5%	23.08%
Not easy to use and compare across different clinical settings (Scalability/ Clinical homogeneity)	3	5.17%	16.67%	0	0%	0%	5	10.2%	41.67%	2	5%	15.38%
Invasive procedure	2	3.45%	11.11%	2	8%	25%	3	6.12%	25%	1	2.5%	7.69%
Data Privacy	2	3.45%	11.11%	2	8%	25%	1	2.04%	8.33%	1	2.5%	7.69%
Other	0	0%	0%	1	4%	12.5%	0	0%	0%	0	0%	0%
Total	58	100%	322.22%	25	100%	312.5%	49	100%	408.33%	40	100%	307.69%

HCPs (reported by 55.36% of respondents), high costs associated with diagnostic procedures (51.79%), and issues related to reimbursement and health insurance coverage (44.64%) (Table 3). These concerns reflect broader systemic limitations in the integration of innovative diagnostic tools into routine clinical practice.

Discussion

The availability of disease-modifying therapies in Europe marks a significant shift in the management of AD, moving toward early and etiology-based diagnosis.[11,12] Early and accurate diagnosis is increasingly recognized as essential for effective patient management, eligibility for emerging treatments such as amyloid-antibody therapies, and the reduction of overall diagnostic costs.[13]

BBMs have demonstrated potential in addressing key challenges in AD care. These include the early detection of individuals at risk, identification of AD onset in patients with subjective cognitive impairment or mild cognitive impairment, differential diagnosis, treatment selection, and monitoring of disease progression.[7,14] The findings of this study reinforce the promise of BBMs as supportive biomarkers for AD as they are viewed favorably by HCPs and biomarker experts.

However, existing diagnostic methods remain invasive, expensive, and inaccessible to many patients, particularly in primary care settings.

This exploratory study highlighted several stakeholder concerns, including doubts about the credibility of diagnostic results, limited knowledge among HCPs, and the invasiveness and cost of current techniques. Perceptions among stakeholders regarding the utility of AD biomarkers are likely shaped by limited experience in this area.

Although the study was designed to capture data from a broad European population, the sample ultimately consisted predominantly of participants from Southern Europe (mainly Greece). The emphasis on cost consideration may be influenced by the geographic distribution of the sample due to the public registration design of the survey. Nonetheless, recent studies suggest that BBMs (e.g., pTau217) may be a comprehensive cost-effective option, potentially reducing the need for expensive imaging and invasive procedures.[15]

Despite BBMs' potential, significant gaps remain in HCP education and awareness, which may hinder the adoption of BBMs and PoC diagnostics. Addressing these gaps through targeted training and awareness campaigns will be critical to the successful integration of new diagnostic methods into clinical workflows.

Emerging technologies such as paper-based lateral-flow assays (LFAs) are gaining attention as potential PoC IVD biosensors.[16,17] These devices offer simplicity, portability, and cost-effectiveness, making them attractive for use in diverse healthcare settings.[18,19] However, paper-based LFAs also face limitations, including low sensitivity, binary output formats, and challenges in handling complex biological samples. These technical constraints must be addressed to enable broader application in AD diagnostics.

This study is the first to gather insights from a diverse group of stakeholders directly and indirectly affected by AD, with the aim of informing the design and development of the 2D-BioPAD paper-based LFA PoC IVD device. Given the small sample size and limited statistical power, the findings should be considered exploratory. These findings will be strengthened through a planned prospective clinical study within the 2D-BioPAD consortium, which will also employ device-experience questionnaires.

This study confirms the growing interest for BBMs in the prognosis, diagnosis, and monitoring of AD. While BBMs offer a promising complementary diagnostic tool to current diagnostic methods, concerns persist regarding cost, invasiveness, and accessibility. Stakeholder feedback suggests that PoC IVD systems incorporating BBMs could help address these challenges, supporting more equitable and timely diagnosis across healthcare settings. These insights will guide the continued development and refinement of the 2D-BioPAD PoC IVD platform, with the ultimate goal of improving diagnostic pathways and outcomes for individuals affected by AD. A key limitation of this study is the limited geographic diversity of the sample, which was consisted mainly by Greek stakeholders across all groups. This concentration may have influenced participants' perspectives regarding issues such as cost, reimbursement, and access to diagnostic services, thereby constraining the generalizability of the findings to other European healthcare contexts.

Acknowledgements

We thank the partners of the consortium and participants of the 2D-BioPAD EU funded project for their cooperation and for data collection, management and proof-reading.

ORCID iDs

Angeliki Koukoura https://orcid.org/0000-0003-3295-8873
Kyriaki Antonopoulou https://orcid.org/0000-0002-9212-737X
Apostolos C Tsolakis https://orcid.org/0000-0003-2606-1402
Alina Solomon https://orcid.org/0000-0002-7166-9903
Magda Tsolaki https://orcid.org/0000-0002-2072-8010
Lutz Froelich https://orcid.org/0000-0003-1494-0813
Anthoula Tsolaki https://orcid.org/0000-0002-5563-7776
Eirini Papadaki https://orcid.org/0000-0003-1513-4645
Efstathios Vassiliadis https://orcid.org/0000-0001-6513-7903
Gitte Juel Holst https://orcid.org/0009-0000-6627-3923

Ethical considerations

No further ethical considerations were noted.

Consent to participate

For the online survey, informed consent was not required due to its design as a publicly accessible registration survey.

Consent for publication

Not applicable.

Author contribution(s)

Angeliki Koukoura: Conceptualization; Data curation; Methodology; Supervision; Writing – original draft; Writing – review & editing.
Kyriaki Antonopoulou: Formal analysis; Methodology; Software; Writing – review & editing.
Apostolos C. Tsolakis: Conceptualization; Writing – review & editing.
Alina Solomon: Conceptualization; Visualization; Writing – review & editing.
Magda Tsolaki: Conceptualization; Visualization; Writing – review & editing.
Lutz Froelich: Conceptualization; Visualization; Writing – review & editing.
Anthoula Tsolaki: Conceptualization; Visualization; Writing – review & editing.
Eirini Papadaki: Resources.
Efstathios Vassiliadis: Conceptualization; Visualization.
Gitte Juel Holst: Project administration; Supervision; Writing – review & editing.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by Horizon Europe Programme 2021–2027 [grant number 101120706].[9]

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data availability statement

The datasets generated and/or analyzed during the current study are available in the Zenodo repository at: https://doi.org/10.5281/zenodo.10974014 and https://zenodo.org/records/15806949.

Supplemental material

Supplemental material for this article is available online.

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