



Deposited via The University of York.

White Rose Research Online URL for this paper:

<https://eprints.whiterose.ac.uk/id/eprint/224653/>

Version: Accepted Version

Article:

Quinn, Steven (Accepted: 2025) The Urgent and Global Need for Democratized Blood-Based Biomarker Diagnostics in Alzheimer's Disease. *The Journal of Precision Medicine: Health and Disease*. ISSN: 3050-6328 (In Press)

<https://doi.org/10.1016/j.premed.2025.100002>

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/>

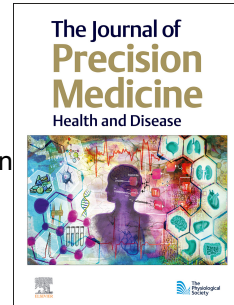
Takedown

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 including the URL of the record and the reason for the withdrawal request.

Journal Pre-proof

The Urgent and Global Need for Democratized Blood-Based Biomarker Diagnostics in Alzheimer's Disease

Steven D. Quinn



PII: S3050-6328(25)00002-2

DOI: <https://doi.org/10.1016/j.premed.2025.100002>

Reference: PREMED 100002

To appear in: *Journal of Precision Medicine: Health and Disease*

Received Date: 17 March 2025

Accepted Date: 17 March 2025

Please cite this article as: Quinn S.D., The Urgent and Global Need for Democratized Blood-Based Biomarker Diagnostics in Alzheimer's Disease, *Journal of Precision Medicine: Health and Disease*, <https://doi.org/10.1016/j.premed.2025.100002>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2025 Published by Elsevier Ltd on behalf of The Physiological Society.

The Urgent and Global Need for Democratized Blood-Based Biomarker Diagnostics in Alzheimer's Disease

Steven D. Quinn^{1,2,*}

¹School of Physics, Engineering and Technology, University of York, Heslington, York, UK. YO10 5DD.

²York Biomedical Research Institute, University of York, Heslington, York, UK. YO10 5DD.

*steven.quinn@york.ac.uk

Alzheimer's disease (AD) represents one of the most pressing healthcare challenges of the 21st century. As a leading cause of dementia, AD impacts over 55 million people worldwide, with this number projected to exceed 139 million by 2050. The economic burden is staggering, with global costs estimated to reach over \$15 trillion, placing immense strain on healthcare systems, patients and caregivers^{1,2}. Despite significant recent progress in understanding the molecular pathology of AD, and in the development of emerging treatments^{3, 4}, access to timely and widespread diagnosis remains a formidable challenge. As a result, many patients are only identified late in the disease course when symptoms are pronounced and neurodegeneration is progressive. This underscores the urgent need for more easily accessible diagnostic tools — particularly those based on blood-based biomarkers — that can facilitate early-stage AD diagnosis, and crucially, enable targeted medical interventions in an accessible and cost-effective way.

The Limitations of Current Diagnostic Strategies

AD is currently diagnosed using a combination of cognitive assessments^{5, 6}, neuroimaging (MRI, PET)⁷, and cerebrospinal fluid (CSF) biomarkers^{8, 9, 10}. While neuroimaging techniques provide valuable insights into disease pathology, they are costly and not widely accessible, particularly in low-resource settings. In the UK, for example, there are only 0.4 PET and 7.4 MRI scanners available per 1 million people. With access limited, the need for democratized diagnostics is clearly highlighted. CSF biomarkers, such as amyloid-beta (A β) and tau proteins, offer robust capabilities to support diagnosis, but with the requirement for invasive lumbar punctures, uptake is low and the procedure is not well suited for routine screening, population or longitudinal monitoring¹¹.

In recent years, blood-based AD biomarkers have offered new promise as tools for diagnosis, and opened the door to the development of minimally-invasive, scalable and cost-effective diagnostic strategies^{12, 13, 14, 15, 16, 17}. Recent breakthroughs have demonstrated that the plasma A β (1-42)/A β (1-40) ratio¹⁸, and levels of plasma-based phosphorylated tau (p-tau217)¹⁶ and neurofilament light chain (NfL)¹⁹ correlate well with CSF and imaging-based biomarkers as well as disease progression. However, translating these discoveries into clinically validated, widely available diagnostic tests is a major technological challenge which requires significant advancements and strategic collaboration across academia, industry and regulatory bodies.

The Role of Blood-Based Biomarkers in Precision Medicine

Precision medicine aims to tailor prevention, diagnosis, and treatment strategies to individual patients based on their biological, genetic, and environmental profiles. Blood-based biomarker diagnostics are critical to realising this paradigm shift in AD management for several reasons. First, plasma biomarkers have shown promise in detecting AD pathology many years before clinical symptoms manifest¹². It follows that identifying individuals at risk before irreversible neuronal damage occurs opens an opportunity for early intervention strategies which could include lifestyle modifications^{20, 21} and

recruitment of patients into clinical trials as new disease-modifying therapies emerge. Second, longitudinal tracking of biomarker levels could provide real-time insights into disease progression and treatment efficacy²². This is especially important as emerging therapies become available. It is also possible that blood test outcomes, in conjunction with other clinical assessments, could guide treatment decisions, and help to optimize patient outcomes. Finally, a significant challenge in AD diagnosis is healthcare disparity, as many patients lack access to specialised centers with neuroimaging and/or CSF analysis capabilities²³. Put simply, blood-based diagnostics, especially those that are as simple to use as a lateral flow device, could democratize AD biomarker detection, making early, accurate and rapid diagnosis feasible across primary and secondary care settings, and, across underrepresented and underserved populations worldwide.

Emerging Technologies for Blood-Based AD Diagnostics

The quest for reliable and accessible blood-based biomarkers for AD has driven the development of increasingly sophisticated and highly sensitive detection platforms capable of detecting low-molecular weight biomarkers at sub-nanomolar levels, all while mitigating against false-positive responses and the complexity that comes with detecting biomarkers within the milieu of blood²⁴. In short, these technologies are transforming the landscape of AD diagnostics.

Among these, the single-molecule array (SIMOA) is a leading platform enabling the digital immunoassay-based detection of plasma proteins at femtomolar concentrations^{25, 26}. However, a suite of additional complementary approaches is emerging, each offering their own unique advantages. For instance, the Multimer Detection System (MDS) can selectively detect various forms of early-stage protein aggregates^{27, 28}, the SomaScan Assay bridges proteomics and genomics, effectively converting protein abundance into quantifiable DNA signals^{29, 30}, and advances in magnetic nanoparticle-based detection approaches have led to the ImmunoMagnetic Reduction Assay which quantifies biomarker abundance via real-time changes in magnetic susceptibility³¹. Electrochemiluminescence immunoassays have also gained traction, as have surface-based sensing approaches which facilitates assessment of the secondary structure of protein biomarkers^{32, 33}. A number of handheld biosensors based on electrochemistry^{34, 35} and photonic³⁶ principles have also recently emerged. Handheld biosensors effectively remove the need for transporting samples and complicated lab-based analysis, and may prove critical as the field moves towards point-of-care diagnostics.

Regardless of the approach or technological innovation, it is clear that the suitability of a blood-based biomarker sensing modality depends on a number of critical factors including scalability, reproducibility, user-friendliness and cost, among others³⁷. In this context it's not yet clear which approach, if any, will ultimately emerge as the "gold standard", or which will be used routinely in healthcare settings and when, but further technology developments, even at the periphery, are necessary as the requirement for multiplexed, ultrasensitive, accessible, reliable and robust diagnostic platforms becomes ever more pressing.

These emerging technologies, primarily developed in research settings, are progressively bridging the gap between laboratory innovation and clinical translation. With further validation and refinement, together with end-user input, they each hold the potential to redefine AD diagnostics.

Challenges and Future Directions

Despite the promise of plasma-based AD diagnostics, several hurdles must be addressed before a more widespread clinical implementation is possible. Clearly, biomarker assays must be rigorously validated across diverse populations and clinical settings to ensure reproducibility and reliability. Contextualizing findings from studies that identify racial differences in biomarker levels will also be of particular

importance as the field develops. Effective clinical adoption of blood-based diagnostics, beyond rigorous regulatory approval, also requires robust infrastructure in place for sample collection, analysis and data interpretation within existing clinical and patient workflows. There are also important ethical and societal considerations regarding early-stage diagnosis that include but are not limited to: the question of when a blood test should be administered; the potential need for patient counselling and monitoring; insurance implications; psychological impact of an early-stage diagnosis; and the need for comprehensive policy frameworks. Addressing these challenges will require sustained investment in technologies that not only demonstrate a high degree of accuracy, reliability and accessibility, but which integrate seamlessly into clinical practice. Moreover, as a community, we also must recognize the importance of developing diagnostic technologies *with* the end-users not simply *for* the end users and in this context, effective patient and public involvement is critical as technologies move from the lab bench into clinical translation.

Conclusion

Developing blood-based biomarker diagnostics for AD represents an exciting paradigm shift in how we approach neurodegenerative disease detection and management. The field is at a tipping point: with new therapies emerging, there is now, more than ever, an urgent and global demand for accelerating technologies for blood-based biomarker detection. By enabling early, accessible and personalized healthcare strategies, these technologies hold potential to transform patient outcomes, but also advance our understanding of AD pathophysiology. Realizing this vision requires continued investment in interdisciplinary research approaches and cross-sector collaborations to bridge the gap between laboratory discoveries and clinical implementation. The future of diagnosing AD early is within reach, and prioritizing assays for blood-based biomarker detection is likely critical to addressing the global burden of dementia in the decades to come.

Acknowledgements

The author thanks the Alzheimer's Society (AS-PG-22-043) for financial support.

References

1. Nandi A, Counts N, Chen S, Seligman B, Tortorice D, Vigo D, *et al.* Global and regional projections of the economic burden of Alzheimer's disease and related dementias from 2019 to 2050: A value of statistical life approach. *EClinicalMedicine* 2022, **51**: 101580.
2. Chen S, Cao Z, Nandi A, Counts N, Jiao L, Prettner K, *et al.* The global macroeconomic burden of Alzheimer's disease and other dementias: estimates and projections for 152 countries or territories. *Lancet Glob Health* 2024, **12**(9): e1534-e1543.
3. Mead S, Fox NC. Lecanemab slows Alzheimer's disease: hope and challenges. *Lancet Neurology* 2023, **22**(2): 106-108.
4. Sims JR, Zimmer JA, Evans CD, Lu M, Ardayfio P, Sparks J, *et al.* Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. *JAMA* 2023, **330**(6): 512-527.
5. Zhuang L, Yang Y, Gao J. Cognitive assessment tools for mild cognitive impairment screening. *J Neurol* 2021, **268**(5): 1615-1622.

6. Curiel Cid RE, Matias-Guiu JA, Loewenstein DA. A review of novel Cognitive Challenge Tests for the assessment of preclinical Alzheimer's disease. *Neuropsychology* 2023, **37**(6): 661-672.
7. Chouliaras L, O'Brien JT. The use of neuroimaging techniques in the early and differential diagnosis of dementia. *Mol Psychiatr* 2023, **28**(10): 4084-4097.
8. Blennow K, Hampel H, Weiner M, Zetterberg H. Cerebrospinal fluid and plasma biomarkers in Alzheimer disease. *Nat Rev Neurol* 2010, **6**(3): 131-144.
9. Bouwman FH, Frisoni GB, Johnson SC, Chen X, Engelborghs S, Ikeuchi T, *et al.* Clinical application of CSF biomarkers for Alzheimer's disease: From rationale to ratios. *Alzheimers Dement (Amst)* 2022, **14**(1): e12314.
10. Papaliagkas V, Kalinderi K, Vareltzis P, Moraitou D, Papamitsou T, Chatzidimitriou M. CSF Biomarkers in the Early Diagnosis of Mild Cognitive Impairment and Alzheimer's Disease. *Int J Mol Sci* 2023, **24**(10).
11. Hampel H, Shaw LM, Aisen P, Chen C, Lleo A, Iwatsubo T, *et al.* State-of-the-art of lumbar puncture and its place in the journey of patients with Alzheimer's disease. *Alzheimers Dement* 2022, **18**(1): 159-177.
12. Hansson O, Blennow K, Zetterberg H, Dage J. Blood biomarkers for Alzheimer's disease in clinical practice and trials. *Nat Aging* 2023, **3**(5): 506-519.
13. Zetterberg H, Apostolova LG, Snyder PJ. Blood-based biomarkers for Alzheimer's disease and related dementias: Keys to success and things to consider. *Alzheimers Dement (Amst)* 2019, **11**: 784-786.
14. Toombs J, Zetterberg H. In the blood: biomarkers for amyloid pathology and neurodegeneration in Alzheimer's disease. *Brain Commun* 2020, **2**(1): fcaa054.
15. Gonzalez-Ortiz F, Kac PR, Brum WS, Zetterberg H, Blennow K, Karikari TK. Plasma phospho-tau in Alzheimer's disease: towards diagnostic and therapeutic trial applications. *Mol Neurodegener* 2023, **18**(1): 18.
16. Ashton NJ, Brum WS, Di Molfetta G, Benedet AL, Arslan B, Jonaitis E, *et al.* Diagnostic Accuracy of a Plasma Phosphorylated Tau 217 Immunoassay for Alzheimer Disease Pathology. *JAMA Neurol* 2024, **81**(3): 255-263.
17. Jack CR, Jr., Andrews JS, Beach TG, Buracchio T, Dunn B, Graf A, *et al.* Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. *Alzheimers Dement* 2024, **20**(8): 5143-5169.

18. Graff-Radford NR, Crook JE, Lucas J, Boeve BF, Knopman DS, Ivnik RJ, *et al.* Association of low plasma A β ₄₂/A β ₄₀ ratios with increased imminent risk for mild cognitive impairment and Alzheimer disease. *Arch Neurol* 2007, **64**(3): 354-362.
19. Mattsson N, Andreasson U, Zetterberg H, Blennow K, Alzheimer's Disease Neuroimaging I. Association of Plasma Neurofilament Light With Neurodegeneration in Patients With Alzheimer Disease. *JAMA Neurol* 2017, **74**(5): 557-566.
20. Ornish D, Madison C, Kivipelto M, Kemp C, McCulloch CE, Galasko D, *et al.* Effects of intensive lifestyle changes on the progression of mild cognitive impairment or early dementia due to Alzheimer's disease: a randomized, controlled clinical trial. *Alzheimers Res Ther* 2024, **16**(1).
21. Dhana K, Franco OH, Ritz EM, Ford CN, Desai P, Krueger KR, *et al.* Healthy lifestyle and life expectancy with and without Alzheimer's dementia: population based cohort study. *Bmj-Brit Med J* 2022, **377**.
22. Yakoub Y, Ashton NJ, Strikwerda-Brown C, Montoliu-Gaya L, Karikari TK, Kac PR, *et al.* Longitudinal blood biomarker trajectories in preclinical Alzheimer's disease. *Alzheimers Dement* 2023, **19**(12): 5620-5631.
23. Balls-Berry JJE, Babulal GM. Health Disparities in Dementia. *Continuum (Minneapolis)* 2022, **28**(3): 872-884.
24. Alvarez-Sanchez L, Pena-Bautista C, Baquero M, Chafer-Pericas C. Novel Ultrasensitive Detection Technologies for the Identification of Early and Minimally Invasive Alzheimer's Disease Blood Biomarkers. *J Alzheimers Dis* 2022, **86**(3): 1337-1369.
25. Li D, Mielke MM. An Update on Blood-Based Markers of Alzheimer's Disease Using the SiMoA Platform. *Neurol Ther* 2019, **8**(Suppl 2): 73-82.
26. Pilotto A, Quaresima V, Trasciatti C, Tolassi C, Bertoli D, Mordenti C, *et al.* Plasma p-tau₂₁₇ in Alzheimer's disease: Lumipulse and ALZpath SIMOA head-to-head comparison. *Brain* 2025, **148**(2): 408-415.
27. An SSA, Lee BS, Yu JS, Lim K, Kim GJ, Lee R, *et al.* Dynamic changes of oligomeric amyloid beta levels in plasma induced by spiked synthetic A β ₄₂. *Alzheimers Res Ther* 2017, **9**(1): 86.
28. Wang SM, Kang DW, Um YH, Kim S, Lee CU, Scheltens P, *et al.* Plasma oligomer beta-amyloid is associated with disease severity and cerebral amyloid deposition in Alzheimer's disease spectrum. *Alzheimers Res Ther* 2024, **16**(1).
29. Sattlecker M, Kiddle SJ, Newhouse S, Proitsi P, Nelson S, Williams S, *et al.* Alzheimer's disease biomarker discovery using SOMAscan multiplexed protein technology. *Alzheimers Dement* 2014, **10**(6): 724-734.

30. Zhao X, Lejnine S, Spond J, Zhang C, Ramaraj TC, Holder DJ, *et al.* A candidate plasma protein classifier to identify Alzheimer's disease. *J Alzheimers Dis* 2015, **43**(2): 549-563.
31. Yang SY, Chiu MJ, Chen TF, Horng HE. Detection of Plasma Biomarkers Using Immunomagnetic Reduction: A Promising Method for the Early Diagnosis of Alzheimer's Disease. *Neurol Ther* 2017, **6**(Suppl 1): 37-56.
32. Kivisakk P, Fatima HA, Cahoon DS, Otieno B, Chacko L, Minooei F, *et al.* Clinical evaluation of a novel plasma pTau217 electrochemiluminescence immunoassay in Alzheimer's disease. *Sci Rep* 2024, **14**(1): 629.
33. Schuler M MM, Langenhoff LC, Budde B, Beyer L, Woitzik N, Gerwert G, Wanka R, Hoeveler A, Dreier M, Hubert D, Galkowski S, Güldenhaupt J, Kötting C, Gerwert KB. A structure-based fluid biomarker for the differential diagnosis of early-stage neurodegenerative diseases measured by the immuno-infrared-sensor (iRS). *Alzheimer's & Dementia* 2023, **19**(S24): e082847.
34. Sharma PK, Kim ES, Mishra S, Ganbold E, Seong RS, Kim YM, *et al.* Ultrasensitive probeless capacitive biosensor for amyloid beta (A β (1-42)) detection in human plasma using interdigitated electrodes. *Biosens Bioelectron* 2022, **212**: 114365.
35. Supraja P, Tripathy S, Singh R, Singh V, Chaudhury G, Singh SG. Towards point-of-care diagnosis of Alzheimer's disease: Multi-analyte based portable chemiresistive platform for simultaneous detection of beta-amyloid (1-40) and (1-42) in plasma. *Biosens Bioelectron* 2021, **186**: 113294.
36. Wijaya SR, Martins A, Morris K, Quinn SD, Krauss TF. Resonant Young's Slit Interferometer for Sensitive Detection of Low-Molecular-Weight Biomarkers. *Biosensors (Basel)* 2025, **15**(1).
37. Krauss TF, Miller L, Walti C, Johnson S. Photonic and electrochemical biosensors for near-patient tests-a critical comparison. *Optica* 2024, **11**(10): 1408-1418.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Journal Pre-proof