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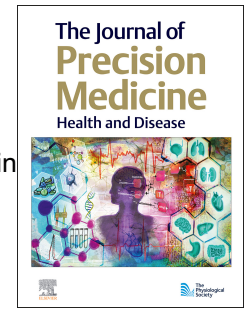

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The Urgent and Global Need for Democratized Blood-Based Biomarker Diagnostics in Alzheimer's Disease

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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 (Aβ) 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 monitoring[11].

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 Aβ(1-42)/Aβ(1-40) ratio[18], 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 manifest[12]. 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 efficacy[22]. 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 capabilities[23]. 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 blood[24]. 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 susceptibility[31]. 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 photonic[36] 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 others[37]. 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.

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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: