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PERSPECTIVE

How can Alzheimer's disease blood-based biomarkers reach clinical practice?

Robert Perneczky[1,2,3,4,5,6] | **Frances-Catherine Quevenco**[7] | **James Hendrix**[7] | **Stephane Epelbaum**[7] | **Charlotte Teunissen**[8] | **Wiesje M. van der Flier**[9] | **Marc Suárez-Calvet**[10,11,12] | **Jiong Shi**[13,14] | **Michelle M. Mielke**[15] | **Takeshi Iwatsubo**[16] | **Sebastian Palmqvist**[17,18] | **Oskar Hansson**[7,17]

[1]Department of Psychiatry and Psychotherapy, LMU Hospital, LMU Munich, Munich, Germany

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

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

[4]School of Public Health, Imperial College London, London, UK

[5]Division of Neuroscience, University of Sheffield, Western Bank, Sheffield, UK

[6]International Registry for Alzheimer's Disease and Other Dementias (InRAD), Deventer, The Netherlands

[7]Eli Lilly and Company, Indianapolis, Indiana, USA

[8]Neurochemistry Lab, Department of Laboratory Medicine, Amsterdam Neuroscience, Amsterdam University Medical Centers, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands

[9]Alzheimer Center Amsterdam, Department of Neurology, Amsterdam University Medical Centers, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands

[10]Barcelonaβeta Brain Research Center, Pasqual Maragall Foundation Barcelona, Barcelona, Spain

[11]Servei de Neurologia, Hospital del Mar, Barcelona, Spain

[12]Hospital del Mar Research Institute, Barcelona, Spain

[13]Department of Neurology, The First Affiliated Hospital of University of Science and Technology, Hefei, Anhui, China

[14]Neurodegenerative Disorder Research Center, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, Anhui, China

[15]Department of Epidemiology and Prevention, Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA

[16]The University of Tokyo, Bunkyo Ward, Tokyo, Japan

[17]Clinical Memory Research Unit, Department of Clinical Sciences in Malmö, Lund University, Johannesgatan, Malmö, Sweden

[18]Memory Clinic, Skåne University Hospital, Malmö, Sweden

Correspondence
Frances-Catherine Quevenco, Eli Lilly and Company Export S.A., Chemin des Coquelicots 16, CH-1214 Vernier, Geneva, Switzerland.
Email: francescatherine.quevenco@lilly.com

Abstract

INTRODUCTION: Alzheimer's disease (AD) diagnosis has been based largely on clinical symptoms, despite their limited sensitivity and specificity. Biomarker use was proposed to support a more accurate and timely diagnosis. However, neuroimaging or cerebrospinal fluid (CSF) is rarely used in primary care due to their perceived invasiveness, cost, and need for appropriate infrastructure. Blood-based biomarkers (BBMs) could represent an economical, minimally invasive alternative, but barriers exist to a seamless translation to the clinic.

METHODS: Ten international experienced AD clinicians and biomarker experts participated in a diagnostic roundtable to discuss the implementation of BBMs for diagnosing early symptomatic AD.

RESULTS: The participants proposed an optimal AD diagnostic pathway and highlighted three main gaps to implementing BBMs for early symptomatic AD diagnosis: limited real-world data, resource gaps, and system barriers.

DISCUSSION: Although BBMs could streamline the AD diagnostic pathway, further real-world evidence and collaboration among multiple stakeholders are needed.

KEYWORDS

Alzheimer's disease, barriers, blood-based biomarkers, diagnosis, diagnostic pathway, guidelines, mild cognitive impairment, population screening

Highlights

- Early symptomatic Alzheimer's disease (AD) diagnosis improves treatment strategy and lowers costs.
- Currently available biomarkers are not widely used across all clinical settings.
- Blood-based biomarkers (BBMs) could be a cost-effective, minimally invasive alternative.
- BBMs could accelerate an accurate AD diagnosis.
- There are barriers to the inclusion of BBMs in clinical practice.

1 | INTRODUCTION

Alzheimer's disease (AD), a chronic progressive neurodegenerative disease, contributes to ≈60%–80% of dementia cases,[1] and is the seventh leading cause of death as well as one of the leading causes of disability globally.[2]

Although the etiopathogenesis of AD is not fully understood, the key pathological hallmarks include the extracellular accumulation of amyloid beta (Aβ) peptides and the formation of neurofibrillary tangles of hyperphosphorylated tau protein.[3] Clinically, AD develops as a spectrum of clinical manifestations that increase in severity over the years, including a stage of mild cognitive impairment, and culminating with mild, moderate, and severe dementia.[4]

AD diagnosis has historically been based on clinical symptoms representing the phase of dementia when the patient has developed a level of cognitive impairment sufficiently severe to impact their capacity to perform daily activities.[4] However, between 25% and 35% of patients with a clinical diagnosis of AD are misdiagnosed in specialized clinics, with an estimated higher percentage in primary care.[5]

Indeed, there are other causes of dementia and cognitive impairment apart from AD,[4] and, therefore, it is fundamental to obtain a timely and accurate diagnosis in the earliest phases of the AD, offering the opportunity to implement a better treatment strategy, reduce societal and caregiver costs, and postpone institutionalization.[6]

Consequently, to provide a more accurate diagnosis of AD, international working groups have proposed to integrate biomarker testing into the clinical assessment of cognitive symptoms.[4,7,8] However, despite the availability of cerebrospinal fluid (CSF) and positron emission tomography (PET) biomarkers to detect AD pathology, they are rarely used in primary routine care, where most patients are diagnosed, due to perceived invasiveness (lumbar puncture), high costs, exposure to ionizing radiation (PET scans), and the need for appropriately equipped facilities.[9]

In contrast, high-performing blood-based biomarkers (BBMs) tests have a sensitivity and specificity of ≈90%.[10] These BBMs could introduce a cost-effective and minimally invasive alternative, with great potential for streamlining the patient journey and enabling timely access to accurate diagnosis, targeted treatment, and better care.[11,12]

Recommended guidelines have been put forward, outlining the preferred product characteristics of BBMs,[13] the minimum acceptable accuracy for their tests,[10] their clinical use,[14] and their implementation into clinical practice.[15] However, crucial barriers to a seamless translation to the clinic remain.

Therefore, an international diagnostic roundtable with 10 experienced AD clinicians and biomarker experts from China, Germany, Japan, The Netherlands, Spain, Sweden, and the United States of America (USA) was organized to propose an optimal pathway for implementing BBMs to ensure timely and accurate diagnosis of early symptomatic AD (outlined in Figure 1). The roundtable discussed implementation of BBM tests to either rule out or rule in AD pathology in both non-specialist and specialist pathways (Figure 1). Furthermore, the roundtable proposed the next steps to streamline the pathway

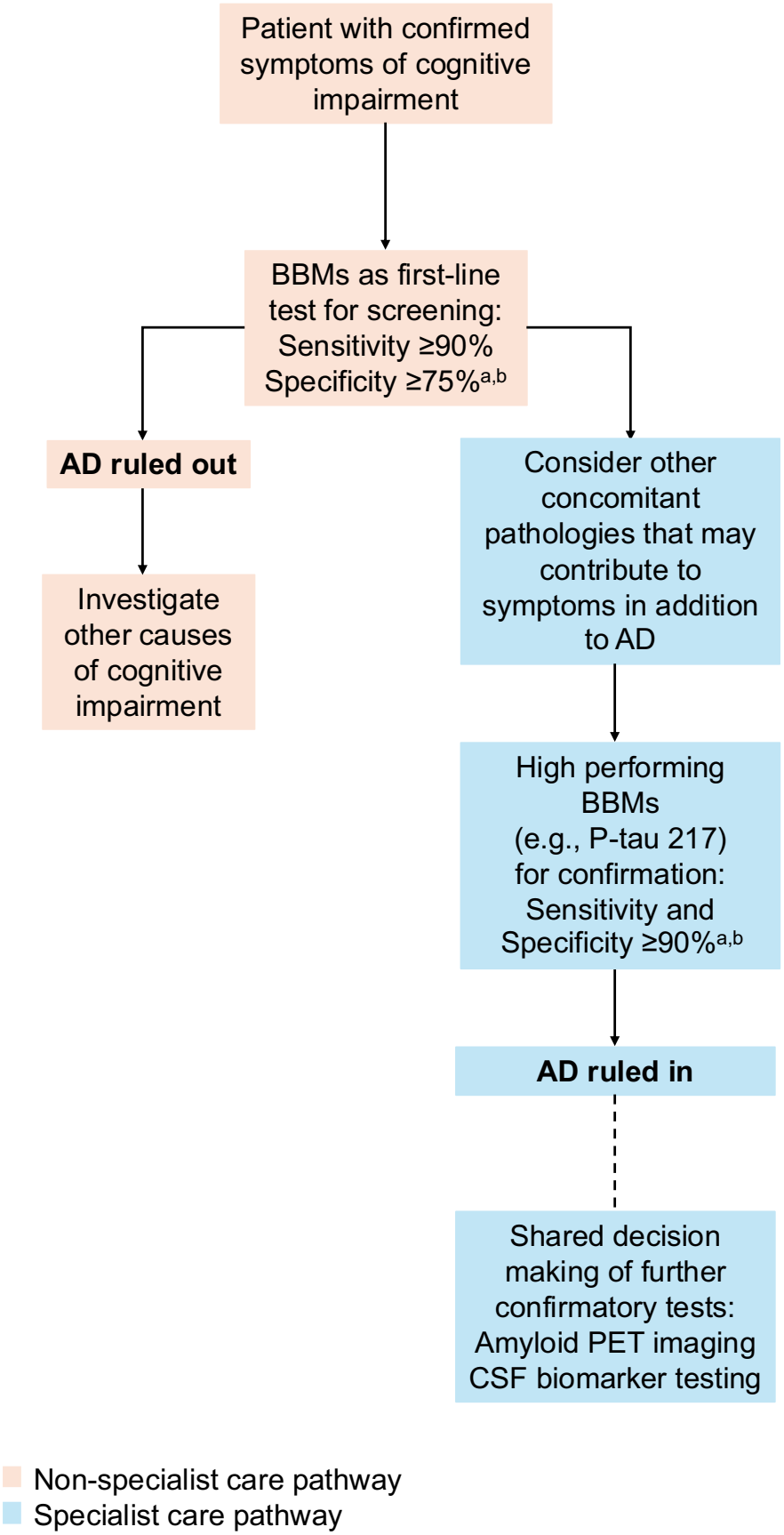

FIGURE 1 Optimal diagnostic pathway for Alzheimer's disease proposed during the diagnostic roundtable. (A) Schindler SE, Galasko D, Pereira AC, et al. Acceptable performance of blood biomarker tests of amyloid pathology—recommendations from the Global CEO Initiative on Alzheimer's Disease. *Nat Rev Neurol*. 2024 Jul;20(7):426–439. (B) Blood biomarkers results must be interpreted in the complete clinical context. AD, Alzheimer's disease; BBMs, blood-based biomarkers.

in clinical practice and highlighted the main barriers to implementing BBMs for AD diagnosis.

2 | ADDING BLOOD-BASED BIOMARKERS TO THE AD DIAGNOSTIC PATHWAY

According to the experts in the roundtable, the integration of BBMs into clinical practice will happen in two phases. In the first phase, two cut-point BBM tests will be implemented by specialists to ensure a high positive predictive value among individuals with cognitive symptoms, as well as a high negative predictive value, and will include an intermediate range (Figure 1). Initially, the diagnosis made with BBMs will be confirmed with CSF or PET, regardless of whether the measurement falls within the intermediate range. Although BBMs tests have the potential to replace confirmatory CSF or PET testing as part of a comprehensive clinical assessment, their acceptance into standard clinical practice will take time, and further evidence from real-world cohorts may support their broader adoption.

A shared decision-making strategy between patient and clinician may additionally be included to further validate the diagnosis of AD using CSF or PET testing (Figure 1).

In the second phase, this optimal diagnostic pathway would also be used routinely in non-specialist care settings to streamline referrals to specialist centers for further testing or treatment.

Indeed, according to a model simulation of the health care system in the USA by Mattke et al., [16] based on the diagnostic performance, referrals using the Mini-Mental State Examination (MMSE) or BBMs alone would increase specialist appointments and waitlists, whereas combining BBMs and the MMSE would reduce the waiting times and potential costs. The potentially reduced waiting time for patient referrals would ensure that specialists dedicate their time to people who have been accurately diagnosed with AD or who have a high likelihood of having the disease.[16]

3 | BARRIERS AND PROPOSED SOLUTIONS

The experts also highlighted three main hurdles to implementing BBMs for the diagnosis of early symptomatic AD: (1) limited real-world data, (2) resource gaps, and (3) system barriers.

3.1 | Limited real-world data

Although studies have been conducted to investigate the effectiveness of BBMs in real-world settings,[17,18] there are limited data on BBM performance in specific patient populations (e.g., cognitively unimpaired, wider range of dementia diagnoses, or patients with concomitant chronic kidney disease, obesity, or other chronic conditions),[19] and racially and ethnically diverse populations.[20–22] This is crucial as the pre-test probability or prevalence of amyloid pathology within a given population could affect the performance of a BBM test.[23]

Therefore, further studies with a more diverse patient population are needed, the results of which can be generalized to all patients with AD. Moreover, there is scarce real-world data on the performance and non-inferiority of BBMs for diagnosing AD in comparison to CSF and PET in prospective studies.[7,19–21] Consequently, additional data are needed to fill this gap.

3.2 | Resource gaps

3.2.1 | Non-specialist health care providers have limited resources to act on cognitive impairment/dementia

Some health care providers (HCPs) do not consider it reasonable to conduct biomarker testing with CSF/PET due to its invasiveness, cost, and perceived low benefit. Moreover, HCPs are often overburdened, with limited time to evaluate the many concerns of their patients.[24]

Some family physicians may skip the initial cognitive assessment due to multiple barriers, such as lack of time and appropriate training, fear of negatively impacting patients with the diagnosis, and of disruption to their own clinical practice.[25] Most physicians would prefer patients with cognitive impairment to be evaluated and followed in their treatment plan by specialists,[26] whereas others do not refer patients as they do not highly estimate the significance of detecting cognitive impairment at the earliest stages of AD. However, the situation could change if the HCPs are provided with tailored education on the importance of detecting the etiology of cognitive impairment in the earliest phases of AD disease,[6] and with innovative and efficient patient pathways for diagnosis and treatment.

In addition, evidence suggests that the pre-test probability of AD is higher in specialized settings.[27] The accuracy of these tests requires knowledge of the disease's prevalence and the clinical and demographic factors that may influence their interpretation.[23] The expected difference in the prevalence of AD in patients with cognitive impairment in primary care compared to specialized settings may therefore result in different negative or positive predictive values for the same test.[27]

To address this, targeted education for HCPs will be necessary to ensure that BBM tests are used appropriately within the intended patient populations for which the assays have been validated for use.

3.2.2 | Lack of, or outdated guidelines, policies, and/or appropriate clinical recommendations

Guidelines and clinical recommendations for AD diagnosis and management differ between countries, with most not reflecting the most recent innovations (e.g., BBM testing), or do not encompass every aspect of this complex and evolving disease thus leaving a serious gap in the available information for HCPs.

Thus, appropriate committees, including specialists and non-specialist HCPs, should develop guidelines and collaborate with

governments to promote awareness and policies that favor the implementation of BBMs in clinical practice. A successful example of this approach is represented by the German National Dementia Strategy, an initiative born in 2020 by the German Federal Government, where specialists proposed measures, and federal states, municipalities, and other non-governmental institutions are implementing them.[28] This strategy is supported by diagnostic and treatment "living guidelines" in a web-based format,[29] allowing for rapid yearly updates to keep up with the increasing pace of innovation in the field, such as developments in BBMs.

3.2.3 | Psychosocial factors

Due to fear, stigma, and lack of perceived benefits in having a diagnosis, patients with AD and their relatives may be reluctant to reach out to specialists to confirm diagnosis and assess the best treatment options.[25] Consequently, a comprehensive educational campaign should be launched for a broad audience.

Another barrier to using BBM tests at scale could be the fear of high societal costs associated with amyloid-targeting therapies. However, a socioeconomic study showed that although the predicted cost for disease-modifying AD treatments is $2.62 trillion, their expected capacity to slow the disease by 30% resulted in a projected gross societal value of $5.5 trillion.[30] Of note, this estimate is at the population level, and the individual costs/benefits are not well understood.

3.3 | System barriers

Although a consensus on minimum performance standards for AD BBMs has been published,[10,13] there are no recommendations in the available clinical guidelines.

Because newly approved in vitro diagnostic tests by the Food and Drug Administration (FDA) in the USA are now available, and further approvals from other regulatory bodies may soon follow,[31] guidelines on how to implement them in clinical practice should be published contemporaneously and easily and quickly updated to accommodate the fast pace of scientific progress in this field, as proposed in the recently published Alzheimer's Association guideline.[27]

Finally, to ensure equitable access to BBMs, reimbursement for these tests will be crucial. Reimbursement from health care systems will need to be supported by studies demonstrating the importance and cost-effectiveness of providing diagnosis and treatment at the earliest stages of AD.

4 | CONCLUSIONS

In conclusion, the following calls to action emerged from the roundtable: First, large-scale international prospective real-world studies are needed to establish the clinical potential of high-performing BBMs for the diagnosis of AD. The inclusion of older, diverse populations and those with multiple chronic conditions is necessary. Second, experts are establishing easy-to-update international and local guidelines that incorporate the tools with sufficient performance to be integrated into leaner, faster AD patient pathways. Third, regulators and payers should approve and provide access to in vitro diagnostic tests that meet the recommended performance criteria, for example, those of the Global CEO Initiative on Alzheimer's Disease on the acceptable performance of BBMs, the Alzheimer's Association clinical practice guidelines, or the World Health Organization (WHO) preferred product characteristics.[10,13,27]

Finally, when these BBMs become available, experts should provide training to HCPs and policymakers on how to implement these new tools in clinical practice and provide the resources to establish referral pathways and expert consultancy systems.

AUTHOR CONTRIBUTIONS

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval to the version to be published.

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ETHICAL APPROVAL

Not applicable.

ORCID

Frances-Catherine Quevenco https://orcid.org/0000-0003-1467-6880

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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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