Review

Current and Future Trends in Biomarkers for the Early Detection of Alzheimer's Disease in Asia: Expert Opinion

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Abstract. Alzheimer's disease (AD) poses a substantial healthcare burden in the rapidly aging Asian population. Early diagnosis of AD, by means of biomarkers, can lead to interventions that might alter the course of the disease. The amyloid, tau, and neurodegeneration (AT[N]) framework, which classifies biomarkers by their core pathophysiological features, is a biomarker measure of amyloid plaques and neurofibrillary tangles. Our current AD biomarker armamentarium, comprising neuroimaging biomarkers and cerebrospinal fluid biomarkers, while clinically useful, may be invasive and expensive and hence not readily available to patients. Several studies have also investigated the use of blood-based measures of established core markers for detection of AD, such as amyloid-β and phosphorylated tau. Furthermore, novel non-invasive peripheral biomarkers and digital biomarkers could potentially expand access to early AD diagnosis to patients in Asia. Despite the multiplicity of established and potential biomarkers in AD, a regional framework for their optimal use to guide early AD diagnosis remains lacking. A group of experts from five regions in Asia gathered at a meeting in March 2021 to review the current evidence on biomarkers in AD diagnosis and discuss best practice around their use, with the goal of developing practical guidance that can be implemented easily by clinicians in Asia to support the early diagnosis of AD. This article summarizes recent key evidence on AD biomarkers and consolidates the experts' insights into the current and future use of these biomarkers for the screening and early diagnosis of AD in Asia.

Keywords: Alzheimer's disease, Asia, AT(N), biomarkers, dementia, early diagnosis

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INTRODUCTION

The population in Asia is a rapidly aging one: it is expected that by 2050, a quarter of the total population in this region will be aged ≥ 60 years [1]. As more individuals live longer than before, Alzheimer's disease (AD) is set to pose a major health problem and substantial healthcare burden.

AD is the most common form of dementia, contributing to 50–75% of dementia cases [1]. Globally, approximately 44 million people live with dementia, with 7.7 million new cases of dementia reported each year; the number of people living with dementia is expected to reach 135 million by 2050 [1]. Meanwhile, in the Asian region, where 48% of the world's demented population now live [2], the number of dementia cases is projected to increase to 71 million by the year 2050 [1]. Furthermore, dementia creates enormous cost to the wider economy: an estimated US$818 million in 2015 alone, and this is projected to increase to US$2 trillion by 2030 [3]. In Asia, dementia care costs are estimated at US$185 billion, with 70% of this amount occurring in advanced economies, which carry 18% of the prevalence [1].

The characteristics and unmet needs of the Asian AD patient are unique. There is growing awareness of the co-existence of AD and cerebrovascular disease (CVD), in which the burden of CVD increases as AD progresses [4]. In a survey conducted by 16 dementia specialists from nine Asia Pacific countries, the co-existence of AD and CVD accounted for 10–20% of all dementia cases in Asia [5]. This high burden of AD and CVD in the Asian dementia population can also further accelerate underlying amyloid and tau pathology, contributing to poor cognitive outcomes [6]. The apolipoprotein E (*APOE*) ε4 allele is the most common genetic variant associated with AD, and its frequency is seemingly dependent on racial and regional differences. Several studies have demonstrated that the frequency of *APOE* ε4 prevalence is lower in people of Asian ethnicity with AD and mild cognitive impairment (MCI) than in their Western counterparts [7, 8]. Moreover, there are unique challenges in the realm of dementia care in Asia, including a limited awareness of and stigma against dementia, as well as inadequate resources to meet the care needs of people living with dementia [1].

AD has long preclinical and prodromal stages during which cognitive decline and pathophysiological changes occur continuously over a period [9, 10]. Although diagnosing dementia is relatively simple, detecting AD at an early stage remains a clinical challenge. The hypothetical models of dynamic biomarkers in AD, introduced by Hadjichrysanthou et al., postulate that markers of amyloid accumulation typically become abnormal first, occurring as early as 30 years before the onset of clinical AD symptoms [9]. A sequence of pathophysiological events then follows, including tauopathy and structural brain changes, before progression to more severe clinical states [9]. In 2018, the National Institute on Aging–Alzheimer's Association (AA) formulated a research framework that defined AD as a biological construct. This framework focuses on the biological diagnosis of AD using the AT(N) classification system: amyloid-β (Aβ) deposition (A), pathologic tau (T), and neurodegeneration or neuronal injury (N); binarizing each of the three biomarker types would thus result in eight biomarker 'profiles' [10]. There has also been evidence that CVD can accelerate AT(N) pathology, contributing to cognitive impairment and increasing neurodegeneration [11]. While a set of appropriate-use criteria (AUC) have been developed to guide the clinical use of amyloid imaging [12] and cerebrospinal fluid (CSF) testing [13] for the diagnosis of AD, these guidelines may not be applicable to Asian populations. Hence, there remains a need for a regional framework to guide the optimal use of biomarkers for early AD diagnosis in Asia.

To address these gaps, experts in AD from five regions in Asia (Hong Kong, Japan [two], Singapore, South Korea, and Taiwan) gathered at a virtual meeting in March 2021 to review the current evidence on biomarkers used in AD diagnosis and discuss best practice around their routine use in clinical practice. The goal of the meeting was to develop practical guidance that can be implemented easily by clinicians across the Asian region to support the early diagnosis of AD. Prior to the meeting, the expert group was also tasked with completing an online survey aimed at understanding current regional practices and perceptions relating to the use of biomarkers for AD screening and early diagnosis (see Supplementary Material).

This paper describes the consolidated guidance and insights into the use of screening and diagnostic biomarkers generated at the meeting.

BIOMARKERS IN THE AD CONTINUUM: CURRENT EVIDENCE AND BEST PRACTICE

The following sections comprise a review of the current evidence around the use of neuroimaging and

fluid biomarkers, as well as novel biomarkers for diagnosis of the AD continuum. The expert group provided recommendations for the use of biomarkers in clinical practice in Asia based on this evidence review and their clinical experience. While the use of some biomarkers is still limited to the research setting, it is the expert group's opinion that these biomarkers will soon have clinical utility.

Neuroimaging biomarkers: Structural imaging

Structural brain imaging techniques support the quantitative characterization of AD and confer benefit in its diagnosis. Computed tomography (CT) and structural magnetic resonance imaging (MRI) are the standard-of-care first-line imaging modalities in AD [14], and both can detect masses, vascular lesions, hemorrhage, and structural abnormalities [14, 15].

CT

In AD, CT may have a role in differential diagnosis, ruling out potentially treatable causes of dementia, such as tumors [16]. The key advantage of CT is that it is readily accessible and less expensive and faster than MRI, making it a valuable diagnostic tool in resource-constrained regions [16] and in those contraindicated for MRI [15].

Structural MRI

Structural MRI is one of the most accessible and widely used neuroimaging techniques in AD diagnosis, with the most commonly used sequences being T1- and T2-weighted volumetric sequences [15]. It is the preferred first-line neuroimaging modality as it can provide a comprehensive overview of structural changes in the brain, including tissue injury, brain atrophy characteristic of neurodegenerative diseases, and CVD [14]. T2-weighted MRI sequences, including fluid-attenuated inversion recovery (FLAIR), are useful in detecting ischemic changes, while T2*- or susceptibility-weighted imaging can identify microbleeds or superficial siderosis, suggestive of sporadic small-vessel disease or cerebral amyloid angiopathy [17]. Recent advances in automatic, volumetric, and machine-learning technologies allow the development of an AD-resemblance atrophy index based on three-dimensional T1-weighted MRI that can reflect the severity and pattern of brain atrophy typical of AD. Such an index was validated using Hong Kong Chinese and Caucasian subjects, which, besides demonstrating excellent sensitivity (92%) and good

specificity (81%) in detecting prodromal AD, also outperformed other conventional MRI markers [18]. Similar technologies have been applied in the differentiation of AD and frontotemporal dementia (FTD), which also showed good performance metrics [19]. Furthermore, diffusion-weighted MRI has been shown to be useful in differentiating AD from cases of rapid cognitive decline suggestive of prion disease [17], such as Creutzfeldt–Jakob disease (CJD) [20]. Notably, a subtype of sporadic CJD shows relatively slow progression characteristic of the AD phenotype [20].

Box 1 | Expert opinion on structural imaging

- While MRI is the preferred first-line neuroimaging modality, there remains a need to establish normative MRI data, such as age-matched normative MRI data, for the Asian region
- CT may be used as the first-line option in resource-constrained settings or in cases in which MRI is contraindicated
- Technology combining automatic, volumetric, and machine learning shows promise in the detection of prodromal AD and in the differentiation of various dementia syndromes

AD, Alzheimer's disease; CT, computed tomography; MRI, magnetic resonance imaging

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Neuroimaging biomarkers: Functional imaging

FDG-PET

Fluorodeoxyglucose positron emission tomography (FDG-PET) is a significant predictive tool for cognitive decline in early-onset AD. As a robust biomarker of overall brain metabolism, it measures glucose use in the brain and can indicate neuronal injury, loss of synaptic activity, and impairment of the blood–brain barrier in AD [15, 21]. FDG-PET has been shown to detect AD with high sensitivity and specificity (>90%) compared with healthy elderly controls and other neurodegenerative conditions such as FTD and dementia with Lewy bodies (DLB) [22, 23]. In a meta-analysis of patients with MCI conducted by Yuan et al., FDG-PET performed better than structural MRI and single-photon emission tomography in predicting conversions to AD [24]. While it may be a useful supplement to current surveillance techniques, FDG-PET is nonetheless relatively expensive, and the requisite for intravenous access and exposure to radioactivity [15] means that its accessibility in Asia remains limited.

Amyloid-PET

Accumulation of Aβ in the brain is considered the first pathological mechanism of AD [10]. As an *in vivo* pathognomonic surrogate for Aβ pathology [15], amyloid-PET measures abnormal deposits of Aβ, whereby elevated levels in the gray matter are consistent with the presence of amyloid plaques, a histopathological hallmark of AD [14]. The Japanese AD Neuroimaging Initiative (J-ADNI) study, which incorporated amyloid-PET with a harmonized protocol from the original ADNI study, revealed comparable rates of amyloid positivity and disease progression in the Asian population with those in the original ADNI population [25]. According to the AUC formulated by the AA and Society of Nuclear Medicine and Molecular Imaging, amyloid-PET is appropriate in individuals with persistent or progressive unexplained MCI or early-onset (≤65 years old) progressive dementia, as well as in patients with atypical or mixed forms of AD [12]. Recent data from a Chinese multicenter study of amyloid-PET in 1193 patients with cognitive impairment (960 with AD, 36 with FTD, 5 with DLB, 144 with MCI, 29 with vascular dementia, 4 with corticobasal syndrome, and 15 with unclassifiable dementia) found that amyloid-PET could be useful for the differential diagnosis of dementia syndromes, particularly in distinguishing AD from FTD [26]. Among the amyloid radiopharmaceuticals that are currently in use, carbon-11 Pittsburgh compound B ($[^{11}C]$PiB) is the most extensively studied [12]. The use of fluorine-18 (^{18}F) ligand, with its longer half-life of 110 min than the 20-min half-life of $[^{11}C]$PiB [12], has facilitated the incorporation of amyloid-PET into research and routine clinical settings in the region.

Tau-PET

In AD, tau pathology is strongly associated with neurodegeneration and cognitive impairment, and tau-PET allows the quantification of tau neuropathology *in vivo*. Postmortem studies have shown that tau-PET is a reliable biomarker of AD neurofibrillary tangles *in vitro*, as measured by disease diagnosis at autopsy, Braak tangle stage, and quantitative immunohistochemistry [27]. First-generation tau-selective PET tracers such as $[^{18}F]$AV1451 [28] can help identify the presence of neurofibrillary tangles, replicating salient features of the Braak histopathological changes; second-generation tau tracers (e.g., $[^{18}F]$MK6240), with higher sensitivity and less off-target binding, are being studied in the research setting [29]. Tau-PET is useful in tracking disease

progression, as evidenced in a longitudinal study of individuals across the AD clinical spectrum in South Korea, Sweden, and the USA. This multicenter study showed that tau-PET not only was an effective prognostic marker in preclinical and prodromal stages of AD, it also outperformed MRI and amyloid-PET in predicting cognitive changes [30].

Box 2 | Expert opinion on functional imaging

- FDG-PET is useful for monitoring progression from prodromal dementia to dementia and for the differential diagnosis of AD
- In resource-constrained settings, FDG-PET would be useful in supporting the diagnosis of AD-type dementia, even though it lacks specificity
- Amyloid-PET is useful for confirming amyloid pathology in MCI and mild dementia, for the differential diagnosis of dementia, and in the detection of AD in young (≤65 years old) patients
- Tau-PET is useful in the differential diagnosis of dementia, as well as to track and predict disease progression
- The expert group predicts that the use of amyloid-PET and tau imaging may be more widespread with the advent of disease-modifying therapies in AD

AD, Alzheimer's disease; FDG-PET, fluorodeoxyglucose positron emission tomography; MCI, mild cognitive impairment

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Fluid biomarkers: CSF biomarkers

Obtained via lumbar puncture, CSF represents an ideal source of AD biomarkers and, given its direct interaction with the interstitial fluid, adequately reflects the milieu of the brain [21]. According to the AUC developed by a group of experts convened by the AA, lumbar puncture and CSF testing for the diagnosis of AD are considered appropriate for patients with subjective cognitive decline and at increased risk of AD; patients with persistent, progressing, and unexplained MCI; patients with symptoms suggestive of AD; patients with MCI or early-onset dementia (<65 years old); patients who meet the core clinical criteria for probable AD with typical age of onset; and patients whose dominant symptom is behavioral change and in whom AD diagnosis is being considered [13].

$Aβ_{42}$, total tau (T-tau), and threonine-181-phosphorylated tau (P-tau181) represent the classical AD CSF biomarkers [31].

$Aβ_{42}$

Aβ is one of the causative proteins of AD, and it is well established that CSF $Aβ_{42}$ is a valid biomarker

for AD diagnosis. Multiple studies have suggested a strong correlation between CSF and PET markers of Aβ [32], and reduced levels of CSF Aβ$_{42}$ is characteristic of preclinical AD and AD dementia [33]. In the J-ADNI study, CSF Aβ$_{42}$ showed a high degree of agreement with the standardized uptake value ratio (SUVr) of amyloid-PET [25]. A trial of CSF Aβ$_{42}$, T-tau, and P-tau in 139 Korean subjects (51 normal controls, 23 MCI, and 65 AD dementia) reported a concordance rate of 92% between CSF Aβ$_{42}$ and amyloid-PET, implying that CSF Aβ$_{42}$ is a viable alternative to amyloid-PET in clinical practice [34]. The CSF Aβ42/Aβ$_{40}$ ratio is also a promising biomarker for AD, believed to control for inter-individual differences in total Aβ levels [33]. With its high sensitivity and specificity in discriminating AD from other forms of dementias [31], the CSF Aβ$_{42}$/Aβ$_{40}$ ratio is superior to Aβ$_{42}$ alone in identifying patients with AD and in predicting disease progression in patients with MCI [31, 33].

P-tau181

CSF P-tau181, which reflects abnormalities of tau metabolism in the brain, has been thoroughly validated as a biomarker of AD and is currently used as a diagnostic criterion in the research setting [35]. Elevated CSF P-tau181 is characteristic of AD dementia and prodromal AD [33, 36], and the combination of increased CSF P-tau181 and low CSF Aβ$_{42}$ is considered a biomarker signature of AD [10, 32]. CSF levels of P-tau181 have been found to be higher in patients with AD than in other tauopathies, such as FTD [37]. In a Japanese cohort of cognitively unimpaired and MCI subjects, the SUVr of tau-PET significantly correlated with levels of CSF P-tau181 [36]. Recently, evidence on another P-tau isoform, tau phosphorylated at threonine 217 (P-tau217), is emerging. The Swedish BioFINDER study cohort (n = 194) demonstrated that CSF P-tau217 performed better than CSF P-tau181 in distinguishing AD dementia from non-AD neurodegenerative disorders, suggesting that P-tau217 may be more useful than P-tau181 in diagnosing AD [35]. Furthermore, a recent study elucidated that CSF P-tau181 and P-tau217 not only mediated the association between amyloid-PET and tau-PET, they also predicted increased tau-PET rates in the cognitively impaired [38].

T-tau

CSF T-tau reflects the intensity of neurodegeneration in AD, whereby elevated levels of CSF T-tau indicate cortical neuronal loss and predict rapid disease progression [33, 37]. A study examining the utility of CSF T-tau in 1031 Japanese subjects (181 normal controls, 366 AD, 168 non-AD dementia, and 316 non-dementia neurological diseases) found that CSF T-tau had a sensitivity and specificity of 59% and 90%, respectively, for the diagnosis of AD [39]. In patients with MCI, CSF T-tau related neurodegeneration mediates the association between P-tau and memory impairment, and while it is a non-specific biomarker within the AD continuum, CSF T-tau provides insights into how early AD pathology affects cognitive outcomes [40]. However, recent evidence has suggested that T-tau in the AD continuum is not associated with neurodegeneration but, rather, with Aβ-mediated abnormal tau metabolism [41, 42].

NfL and neurogranin

Neurofilament light protein (NfL) is a sensitive marker of neuroaxonal damage in a variety of neurological disorders; it is increasingly being employed to predict dementia and stratify AD dementia risk [43]. When used alongside MRI, CSF NfL may have potential as a prognostic biomarker to help track AD neurodegeneration [44]. CSF NfL concentration is increased in early AD and is correlated with cognitive decline and structural brain changes in patients with MCI [44]. While elevated CSF NfL is predictive of neurodegeneration, it is not a feature specific to AD [43].

Neurogranin is a post-synaptic protein that is abundantly expressed in the brain [33]. Elevated levels of CSF neurogranin is specific to AD and prodromal AD and may serve as a biomarker of synaptic dysfunction and degeneration [33]. Besides, increased CSF neurogranin is predictive of cognitive deterioration and hippocampal atrophy over time [33] and may be useful in the stratification of dementia risk in patients with amyloid and/or tau pathology.

Fluid biomarkers: Blood-based biomarkers

With blood being more accessible than CSF, blood or plasma sampling may be preferable to CSF collection. However, as many proteins and other substances are present in the bloodstream [33], measuring AD biomarkers in the blood requires sensitive and specific immunoassays and careful validation, and further real-world validation is required before its routine clinical use. Here we summarize the current knowledge on blood-based biomarkers with respect

Box 3 | Expert opinion on CSF biomarkers

- CSF Aβ_{42} and P-tau181 are useful for detecting early-onset AD (<65 years old) and the differential diagnosis of AD
- CSF Aβ_{42}/Aβ_{40} ratio is valuable for the identification of AD and differential diagnosis, as well as the prediction of progression in people with MCI
- Other CSF biomarkers, such as CSF neurogranin, may be used to stratify dementia risk in patients with amyloid and/or tau pathology
- A combination of biomarkers (imaging and CSF) for amyloid deposition, tauopathy, and neurodegeneration has value in predicting risk of dementia in people with MCI [45]
- CSF collection is accompanied by an invasive lumbar puncture procedure [31], which may prevent its use as a screening tool in early AD. It may be even more difficult to justify its repeated use for monitoring disease progression. Nonetheless, CSF sampling may have an advantage over PET as multiple assessments can be easily incorporated with CSF samples. Also, while amyloid-PET is minimally invasive, it is an expensive and scarcely available procedure in the region
- There remains a need to establish standardized protocols for CSF biomarker collection (methods and timing of collection) and evaluation, as well as normative data for the Asian population

AD, Alzheimer's disease; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; P-tau181, threonine-181-phosphorylated tau; PET, positron emission tomography

to their potential role in identifying individuals at risk of AD.

Aβ

In recent studies, plasma Aβ levels have exhibited correlation with Aβ levels in the CSF and brain Aβ burden [33]. However, while low plasma Aβ_{42} and Aβ_{42}/Aβ_{40} ratio have been linked to brain amyloidosis, these markers do not yet demonstrate diagnostic value in AD [33]. The measurement of oligomeric Aβ in the plasma, a substance toxic to synapses, represents a non-invasive, inexpensive, and accessible method for AD diagnosis. In a study by Wang et al., plasma levels of Aβ oligomers, measured using a multimer detection system (MDS), were higher in patients with AD than in normal controls, and they correlated well with conventional AD biomarkers [46]. In 2019, Palmqvist et al. demonstrated that the diagnostic accuracy of plasma Aβ_{42}/Aβ_{40} is improved when coupled with *APOE* genotype analysis [47]. Taken together, the goal would be to develop a screening algorithm based on plasma Aβ, tau, and neurodegeneration biomarkers to identify individuals in the primary care setting who could be referred for further testing using CSF biomarkers and PET imaging [33].

P-tau

Studies on plasma P-tau have reported findings on their diagnostic and prognostic accuracy. Plasma P-tau181, which increases with AD clinical severity [48], is a promising new biomarker candidate for AD diagnosis and prognosis. Besides being associated with the subsequent development of AD dementia, P-tau181 also effectively and accurately differentiated AD dementia from other neurodegenerative disorders [48]. In a recent trial of 451 Chinese subjects (320 with cognitive impairment and 131 cognitively normal) from a memory clinic and a community cohort, plasma P-tau181 proved to be a promising, clinically relevant blood-based biomarker, having correlations with broader cognitive domains compared with plasma Aβ, NfL, and T-tau [49]. Another plasma P-tau, P-tau217, has emerged as the most robust blood-based biomarker for AD yet. Plasma P-tau217 performed better than plasma P-tau181, plasma NfL, and MRI in differentiating AD dementia from other neurodegenerative diseases, and it was similar to key CSF- or PET-based measures [35].

NfL

NfL is a recognized biomarker for neurodegeneration and can also be assessed in the blood. Research has revealed that levels of NfL in the blood and CSF are highly correlated [50]. Recently, it has been demonstrated that the dynamics of serum NfL predicted neurodegeneration and clinical progression in pre-symptomatic patients with familial AD, in which the rate of change in serum NfL was significantly higher in mutation carriers relative to non-mutation carriers [50]. Furthermore, in this same study, serum NfL concentrations were also associated with global cognitive status (as assessed by the Mini-Mental State Examination and Logical Memory Test) [50]. However, it is important to note that elevated serum NfL is not a feature specific to AD; it is found in many neurodegenerative diseases [50], such as FTD. In this context, and given the strong association between NfL levels in the CSF and blood, serum NfL may be positioned as a non-invasive and cost-effective tool to screen for neurodegeneration [33] and monitor disease progression [43].

Prospective biomarkers of AD

The race towards confirming novel biomarkers in AD is a fast-paced one, particularly in the current age of precision and personalized medicine. In the following section, we discuss current, non-invasive,

Box 4 | Expert opinion on blood-based biomarkers

- While blood-based biomarkers are currently limited to the research setting, in general, they are useful for screening and stratifying AD, monitoring disease progression, and predicting therapeutic response to DMT. They are more easily assessable than CSF biomarkers, especially for repeated assessments
- The plasma $A\beta_{42}/A\beta_{40}$ ratio, P-tau181, and P-tau217 have the potential for triaging patients in the primary care setting for further testing using PET imaging or CSF biomarkers
- Plasma P-tau181 and P-tau217 have a potential role in stratifying risk of progression from prodromal dementia to AD dementia
- Plasma NfL is a biomarker for neurodegeneration in several cognitive disorders and may be a feasible screening test and tool to monitor disease progression
- The expert group highlights the need for fluid biomarkers to undergo a phase of standardization to harmonize assay platforms and define Asian reference and cut-off values
- A panel of fluid biomarkers reflecting amyloid and tau pathology, as well as neurodegeneration, would be imperative for the application of these blood tests in research and clinical practice
- If accurate blood-based biomarkers are made available at a reasonable cost to patients, they may become a standard part of the dementia workup to predict risk and screen for AD
- Blood-based biomarkers may offer an opportunity for greater health equity, facilitating research into AD progression across larger and more representative populations

AD, Alzheimer's disease; CSF, cerebrospinal fluid; DMT, disease-modifying therapy; NfL, neurofilament light protein; PET, positron emission tomography; P-tau181, threonine-181-phosphorylated tau; P-tau217, tau phosphorylated at threonine 217

and investigational biomarkers that may have important roles to play in the research and diagnosis of AD in the near future.

Digital biomarkers

Digital biomarkers refer to medical data that are collected through digital technology, such as mobile and wearable devices. In AD, and particularly in Asia, where there is a significant rise in the adoption of digital technology and level of digital literacy [51], readily accessible digital biomarkers represent a feasible alternative to classical biomarkers in capturing complex everyday activities, besides being a sensitive disease predictor [52]. Digital biomarkers offer the potential to collect continuous data, by means of active or passive measurements, and to detect and monitor disease. Gamified digital interventions could play a role in measuring performance on cognitive evaluations, or assessing executive function and psychomotor processing speed through reaction or

latent time, helping to detect subtle cognitive changes and enhancing the early detection of AD [53]. Furthermore, advanced analytic platforms that employ artificial intelligence (AI) are also able to process digital biomarker data from multiple sources and generate insights into behavioral changes and cognitive decline that correlate with clinical observations and laboratory biomarkers [52]. Despite their potential, digital biomarkers and their endpoints need to be validated, and the data generated should be clinically relevant across various patient populations [52].

Novel non-invasive biological setups

Several potential biomarkers in easily accessible and non-invasive biofluids have displayed potential in characterizing the pathological hallmarks of AD and supporting the early diagnosis and prognosis of AD. AD-related biomarkers have been reported in saliva: the relationship between levels of salivary Aβ, tau, and lactoferrin (a peptide detected in senile plaques, neurofibrillary tangles, and microglia in AD brains) and AD progression shows that saliva is a potential source of biomarkers for AD and MCI [21] and supports the need for further studies on its viability in the dementia setting. In urine, several proteins and metabolites, such as apolipoprotein C3 (APOC3) [54], are involved in the pathological processes of AD, warranting further analysis of urinary biomarkers for AD. Besides saliva, tear fluid is also a viable source of biomarkers, containing proteins such as lipocalin 1 and lysozyme C, which are involved in a slew of immune and inflammatory processes [55]. Light-induced pupillary responses and macular ganglion cell–inner plexiform layer thickness have also been considered biomarker candidates for early AD diagnosis [56], but the impact of the disease on these parameters remains controversial.

Neuroinflammation biomarkers

Neuroinflammation is a pathological hallmark of MCI and AD. Several biomarker candidates of neuroinflammation, for example, high-mobility group box 1 (HMGB1) [57] and translocator protein (TSPO)-PET imaging [58], have been extensively investigated in AD patients. However, as neuroinflammation alone is not a marker of specific pathology, its biomarkers have limited diagnostic value in AD.

Genetic markers

Several target genes and proteins contribute to the etiology of AD. *APOE ε*4 is a major genetic risk fac-

tor for AD, and carriers of the *APOE ε4* gene are more likely to develop AD [59]. However, it is important to note that the *ε4* allele is insufficient to cause AD, and its contribution to AD burden also differs by ethnic group: the risk associated with the allele may be lower among Asian populations with lower prevalence of *APOE ε4* than among those in the West [7]. Nonetheless, an *APOE ε4* genetic risk test in combination with other blood-based biomarkers may be useful for the screening of AD [47], as well as being a predictive factor for treatment safety when prescribing disease-modifying therapies (DMTs) [60]. Besides *APOE ε4*, sortilin-related receptor 1 (*SORL1*) has also emerged as a major AD risk gene. A recent study reported that variants of the *SORL1* gene increased the risk of late-onset AD in Japanese, Korean, and Caucasian populations [61]. Zhou et al. showed that *SORL1* was also associated with AD in the Hong Kong Chinese population. Additionally, based on common genetic variants selected from this population, a polygenic risk score model was constructed, in which the score outperformed the *ε4* allele in predicting AD risk among Chinese subjects [62]. Furthermore, there is growing interest in microRNAs (miRNAs), which play a critical role in the pathogenesis of AD. miRNAs are attractive candidates for blood-based biomarkers to characterize AD, and in a Japanese study, the miRNA miR-501-3p, with its remarkable upregulation in AD brains, strongly suggests a role as a novel blood-based biomarker for AD [63].

EEG

Electroencephalography (EEG) is a non-invasive, cost-effective, and widely available method of measuring temporal behaviors of neural activity, reflecting cortical neuronal functioning. It can be used in combination with other modalities to track and predict disease progression in routine clinical settings [64].

Advanced imaging modalities

As functional brain changes are thought to precede structural brain alterations, functional MRI (fMRI) is considered a promising biomarker in AD as it provides useful information about the functional integrity of brain networks through blood oxygenation level-dependent (BOLD) signals. fMRI can detect AD-related early brain dysfunction and monitor treatment response, which may be instrumental to the evaluation of DMTs in the near future [15]. Diffusion tensor imaging is an MRI-based technique capable of probing the microstructural integrity

of white matter. However, as it is particularly sensitive to motion and has comparatively long scan times, it may not be well suited for clinical use [65].

Box 5 | Expert opinion on prospective biomarkers

- Non-invasive and easy-access biological setups remain as potential proxies for blood-based biomarkers in the detection of cognitive impairment. Future studies should explore whether a combination of non-invasive biomarkers is superior to single biomarkers in the early detection of AD
- Digital biomarker technologies have a role in improving access to AD screening, diagnosis, and monitoring of disease progression. They can be used at home and in tandem with other physical activity tracking or monitoring devices. While cost effective, they have a high logistical burden in that they would need to be validated, standardized, and adapted to various language and cultural requirements
- AI-supported continuous data and algorithms have value in monitoring disease progression and helping to predict AD dementia. The post-processing of imaging data and quantitative aspect of AI may help to identify subtle changes and atrophies in the brain that are typical of AD
- Novel biomarkers for neuroinflammation may be useful for the differential diagnosis and staging of AD, but their utility in clinical practice remains inconclusive
- The *APOE ε4* genetic risk test, in combination with other blood-based biomarkers, may have value in the screening of AD and in predicting treatment safety with DMTs
- Although polygenic risk score models may be promising in the detection of AD, different risk scores may need to be developed for different ethnic groups in the region
- EEG with special analysis algorithms may be useful for screening, diagnosis, and progression tracking in AD, but there is currently no recommendation for its routine use in clinical practice
- The clinical applicability of advanced imaging modalities remains limited in the Asian region because of prohibitive costs and complex follow-up assessments

AD, Alzheimer's disease; AI, artificial intelligence; *APOE ε4*, apolipoprotein E *ε4* allele; DMT, disease-modifying therapy; EEG, electroencephalography

CONCLUSIONS

It is important to recognize AD as a multifactorial disease, and a combined approach with imaging and fluid biomarkers that reflect disease pathogenesis is a crucial step in the early diagnosis of AD. In the Asian region, however, the use of AD biomarkers for early diagnosis has been limited.

The recent approval of aducanumab by the US Food and Drug Administration not only marks a watershed in the treatment of early stages of AD and the prevention of progression to clinical dementia, it also paves the way for more innovation in AD. These advancements signal the pertinence of biomarker

testing in that biomarker testing may become routine in clinical practice for efficient diagnosis of AD and MCI; minimally invasive procedures and readily accessible biomarkers, such as blood-based biomarkers, will be appreciated. Also, with the arrival of DMTs, the number of patients eligible for treatment would be substantial because of the large reservoir of prevalent cases in Asia [2]. Healthcare systems in Asia should therefore be prepared to adapt and incorporate routine biomarker testing into clinical practice. Additionally, given the potential biological uniqueness of the Asian AD population, it is imperative that biomarker-supported clinical trials with DMTs be conducted not only to evaluate the efficacy and safety of DMTs in Asian patients, but also to provide information for effective biomarker algorithms. Moreover, the proliferation of smart devices in some countries in Asia makes the region well placed for research around the use of digital biomarkers and AI-driven technologies for AD.

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CONFLICT OF INTEREST

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SUPPLEMENTARY MATERIAL

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