General Psychiatry

Consensus on rapid screening for prodromal Alzheimer's disease in China

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To cite: Huang L, Li Q, Lu Y, *et al*. Consensus on rapid screening for prodromal Alzheimer's disease in China. *General Psychiatry* 2024;**37**:e101310. doi:10.1136/gpsych-2023-101310

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/gpsych-2023-101310).

Received 31 August 2023
Accepted 19 December 2023

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ABSTRACT

Alzheimer's disease (AD) is a common cause of dementia, characterised by cerebral amyloid-β deposition, pathological tau and neurodegeneration. The prodromal stage of AD (pAD) refers to patients with mild cognitive impairment (MCI) and evidence of AD's pathology. At this stage, disease-modifying interventions should be used to prevent the progression to dementia. Given the inherent heterogeneity of MCI, more specific biomarkers are needed to elucidate the underlying AD's pathology. Although the uses of cerebrospinal fluid and positron emission tomography are widely accepted methods for detecting AD's pathology, their clinical applications are limited by their high costs and invasiveness, particularly in low-income areas in China. Therefore, to improve the early detection of Alzheimer's disease (AD) pathology through cost-effective screening methods, a panel of 45 neurologists, psychiatrists and gerontologists was invited to establish a formal consensus on the screening of pAD in China. The supportive evidence and grades of recommendations are based on a systematic literature review and focus group discussion. National meetings were held to allow participants to review, vote and provide their expert opinions to reach a consensus. A majority (two-thirds) decision was used for questions for which consensus could not be reached. Recommended screening methods are presented in this publication, including neuropsychological assessment, peripheral biomarkers and brain imaging. In addition, a general workflow for screening pAD in China is established, which will help clinicians identify individuals at high risk and determine therapeutic targets.

INTRODUCTION

Alzheimer's disease (AD) is a common neurodegenerative disease that causes cognitive impairment in older adults, characterised by a series of pathological processes including the formation of amyloid-β plaques, hyperphosphorylation of tau proteins aggregated in neurofibrillary tangles, neuroinflammation and cell death. Mild cognitive impairment (MCI) is usually considered the (pAD), which refers to individuals with cognitive impairment that is not severe enough to result in a significant functional impact on daily activities.

China has the largest patient population of AD in the world, imposing a heavy social and economic burden on public health.[1 2] In China, there were 9.83 million people aged ≥60 years with AD and 38.77 million with MCI.[3] With the ageing population, the incidence is increasing rapidly, and the ranking of deaths due to AD in China rose from 10th in 1990 to 5th in 2019.[4] The overall economic cost of AD in China was US$167.7 billion in 2015, which is expected to reach US$1.8 trillion by 2050.[5] Despite the high prevalence and cost, diagnostic techniques and management strategies for AD in China are still inadequate, especially in rural areas. Efforts should be made to establish a screening flowchart for the early stages of AD using more efficient and inexpensive methods.

The neuropathological changes in AD can last for decades before the development of measurable cognitive symptoms, and timely intervention may delay the cognitive decline. To discover interventions that can prevent or delay the initial onset of AD, much attention should be paid to the predementia stage.

According to the 2018 National Institute on Aging-Alzheimer's Association (NIA-AA) research framework, a biological definition of AD is established based on the AT(N) biomarkers.[6] Biomarkers are grouped into those of amyloid-β deposition (A), pathological tau (T) and neurodegeneration (N), measured by positron emission tomography (PET), cerebrospinal fluid (CSF) and MRI. The cerebral deposition of amyloid-β protein is believed to be the core of AD's pathogenesis, and an individual with biomarker evidence of amyloid-β deposition alone would be classified as having 'AD's pathologic change'.[6]

The cognitive symptoms of AD's continuum are divided into six stages. Stage 1 is defined by biomarker evidence of AD in asymptomatic individuals. Stage 2 describes the earliest detectable clinical symptoms, including subjective cognitive

decline (SCD), objectively defined subtle cognitive decline (obj-SCD) and neurobehavioural changes alone. Stages 1 and 2 both describe the preclinical phase of AD. Stage 3 refers to MCI. Stages 4–6 refer to mild, moderate and severe dementia, respectively.

The 2021 International Working Group (IWG) recommendations on the clinical diagnosis of AD introduce the concept of pAD, which refers to the early symptomatic and predementia phase and mainly includes the stage of MCI.[7] The 2018 NIA-AA and 2021 IWG criteria both require AD's pathologies for accurate diagnosis.

Since antiamyloid monoclonal antibodies have statistically improved cognitive and biomarker outcomes in recent AD phase III clinical trials, early and accurate identification of patients with positive amyloid-β deposition (Aβ+) becomes increasingly important. However, although PET and CSF are valid proxies for detecting AD's pathology, they are either expensive or invasive. Meta-analysis showed the prevalence of Aβ+ in the AD population varied across different studies, and the number of patients at predementia stages remains uncertain in low- and middle-income regions where biomarker studies are missing.[8 9] This highlights the need for less expensive and more widely accessible screening methods to identify individuals at risk for pAD in China.

Based on this background, the current consensus intended to recommend effective and cost-saving screening approaches to identify individuals at high risk of AD, particularly those with pAD. It should also be noted that the current consensus is not proposing methods that can fully replace amyloid-PET or CSF, but suggesting several options to flag individuals at-risk that warrant further diagnostic testing and avoid unnecessary examinations.

MATERIALS AND METHODS

A panel of 45 neurologists, psychiatrists and gerontologists (see the Acknowledgements section) was invited to review literature, vote and provide their opinions to reach this consensus. A majority (two-thirds) decision was used for topics for which consensus could not be reached. All members were required to disclose any conflicts of interest that may have a direct regulatory or commercial impact resulting from the publication of this consensus. No commercial funding was provided to support the literature review or the preparation of this paper.

Systematic literature search

We conducted a systematic literature review for promising pAD screening methods in the last 20 years. The PubMed database was used to search the literature for current screening methods related to pAD. The final search encompassed papers published from 2003 to 2023 (conducted on November 29, 2023) and was limited to clinical trials, meta-analyses, practice guidelines and research in humans, supplemented by major presentations at international meetings where abstracts were peer reviewed. The search terms included 'prodromal Alzheimer's disease', 'mild cognitive impairment', 'neuropsychological assessment', 'digital tests', 'blood tests', 'brain imaging', 'biomarkers', 'screening methods' and 'early diagnosis'. The search resulted in the retrieval of nearly 3000 manuscripts, which were screened by experts to include only articles with clinically accurate and relevant information and to remove duplicate papers, resulting in a final bibliography of 124 manuscripts.

Consensus statements and evidence-level categorisation

Following comprehensive discussion at national meetings, we achieved an expert consensus on the rapid screening of pAD, including neuropsychological assessment, peripheral biomarkers and brain imaging.

Levels of evidence are based on the Oxford Centre for Evidence-Based Criteria: Ia, systematic review of randomised controlled trials (RCTs) with homogeneity; Ib, individual RCT; Ic, all or none; IIa, systematic review of cohort studies with homogeneity; IIb, individual cohort study; IIc, outcomes research; IIIa, systematic review of case-control studies with homogeneity; IIIb, individual case-control study; IV, case series; V, expert opinion.

Grades of commendation include: A, consistent level 1 studies; B, consistent level 2 or 3 studies or extrapolations from level 1 studies; C, level 4 studies or extrapolations from level 2 or 3 studies; D, level 5 evidence or troublingly inconsistent or inconclusive studies of any level.

DATA ANALYSIS

Neuropsychological evaluations

Recent developments in the field of cognitive testing have led to a growth of methodologies showing potential for pAD assessment, including conventional paper-and-pencil tests, assessment of metacognition, electronic cognitive assessment tools and digital behavioural markers. Non-cognitive assessment scales are also important for the clinical diagnosis of AD, such as the Activities of Daily Living Scale, Functional Activities Questionnaire, Hamilton Depression Scale, Hamilton Anxiety Scale and Neuropsychiatric Inventory, but their value in detecting pAD remains unclear.

Conventional paper-and-pencil tests

Traditional cognitive tests are the basis of clinical diagnosis. Several paper-and-pencil tests are widely used for the screening of MCI and dementia, such as the Mini Mental State Examination (MMSE), the Montreal Cognitive Assessment (MoCA) or MoCA Basic version, and the Third version of Addenbrooke's Cognitive Examination.[10–13] The effectiveness of these

traditional tests to diagnose MCI is summarised in table 1.

Some cognitive tests are used for the evaluation of various cognitive domains, including the auditory verbal learning test (AVLT), Boston naming test, verbal fluency test, symbol digit modalities test and trail making test to assess the abilities of memory, language, attention and executive function, respectively. Meta-analysis showed that cognitive impairment related to amyloid-β is usually observed in semantic memory, visuospatial function and episodic memory, but such impact cannot identify the presence of amyloid-β deposits.[14]

Promising developments in the neuropsychological paradigm stress their association with biomarkers. For example, the visual short-term memory binding test,[15] the Loewenstein-Acevedo Scales for Semantic Interference and Learning[16] and the category switching test (CaST)[17] have been reported to correlate strongly with cerebral amyloid burden (table 1). These tests rely on contextual information to support memory encoding and retrieval, semantic binding and controlled learning, which have recently demonstrated their use for the assessment of amyloid deposition[18] and can be classified as 'Aβ+ sensitive' tests.

Metacognition

Metacognition reflects an individual's reflection, regulation or evaluation of their knowledge or cognitive activity.[19] As a core component of metacognition, metamemory represents an individual's self-awareness and self-monitoring of memory activities. Approximately 80%–93% of MCI and mild AD cases have impaired metacognitive function.[20 21] Previous research reported that decreased metacognition is associated with the accumulation of amyloid-β and tau proteins, as well as reduced brain metabolism and disturbed network connectivity.[20 22–25]

There are two key methods to evaluate metacognition. The first method indicated as 'performance discrepancy' is based on the discrepancy between the patient's actual performance and their estimation scores on a certain neuropsychological test, which is usually combined in the semantic or episodic memory tasks,[19] such as feeling of knowing judgements,[26] judgement of learning[27 28] and degree of confidence (DOC).[29] The second method is 'patient-informant discrepancy', which is based on the calculation of discrepancy scores between questionnaires for the patient and their caregivers, such as the Everyday Cognition Scale,[30] Measurement of Anosognosia Instrument[31] and Memory Awareness Rating Scale.[32]

The presence of impaired metacognition in patients with MCI may be a risk factor for the transition to dementia, with individuals exhibiting this impairment being nearly three times more likely to progress to dementia within 2 years.[33] In the preclinical phase of AD, some individuals may reflect a high level of awareness of subtle cognitive decline, evidenced by increased cognitive complaints, and this awareness declines as the disease continues to progress. Both longitudinal and cross-sectional studies have found that metamemory impairment precedes objective cognitive decline in Aβ+ patients.[29 34]

Previous studies reported that metamemory impairment occurs approximately 1.6 years before the diagnosis of MCI in Aβ+ patients,[34] whereas the decline of anosognosia or metamemory can be detected approximately 3–4 years before reaching the clinical diagnosis of AD.[34 35] Patients with MCI with metacognition deficit often exhibit overconfidence in their actual performance, such as making overestimated judgement in episodic memory tasks.[29] The DOC,[29] a subset of AVLT Huashan version, is sensitive to detecting SCD individuals with Aβ+ and warrants larger trials for further confirmation in the Chinese population. We summarised the current literature on metacognition for detecting pAD in table 1.

Electronic assessment tools

Electronic assessment tools are delivered by automated and intelligent cognitive measures, including the translation of existing standardised paper-and-pencil tests into computerised administration, and the development of novel electronic batteries based on promising techniques in neuropsychological approaches for the detection of cognitive impairment. We listed several commonly used electronic neuropsychological assessment tools that have been reported to be effective in screening for early cognitive impairment (table 1).

The advantages of electronic assessments include comprehensive documentation of both response speed and accuracy, independence from assessors, convenient data storage and remote administration. However, some electronic assessments still require manual assistance, and unfamiliarity with electronic devices may impact test results and lead to lower completion rates in populations with a lack of interest.

The digital clock-drawing test (DCTclock) has been found to be associated with abnormal amyloid and tau protein, with better discrimination ability than standard neuropsychological assessments such as the Preclinical Alzheimer Cognitive Composite (PACC). The DCTclock showed good discrimination performance between Aβ± cognitively normal groups with an area under the receiver operating characteristic curve (AUC) of 0.72, better than PACC (AUC=0.63) and hand-scored clock (AUC=0.58).[36]

The Brain Health Assessment (BHA) takes about 10 min to complete and consists of three subtests. The BHA subtests of Favorites (measuring associative memory), Match (measuring executive functions and speed) and Everyday Cognition Scale were observed to be significantly associated with Aβ+ (AUC=0.75).[37]

The Cogstate Brief Battery (CBB) takes about 10 min to complete, contains four individual card tasks and measures psychomotor function, attention, working memory and visual recognition memory. The CBB Learning/Working Memory Composite Score could discriminate between

Table 1 Effectiveness of different cognitive assessments for detecting mild cognitive impairment (clinical diagnosis) and prodromal Alzheimer's disease

Instruments	Subjects	Type of study	Author (year)	Results
Paper-and-pencil tests				
MMSE	280 NC, 264 MCI	Cross-sectional	Chen *et al* (2016)[10]	AUC=0.72–0.80 to screen for patients with MCI according to different education levels.
	431 NC, 285 MCI	Cross-sectional	Pan *et al* (2022)[12]	AUC=0.76–0.82 to screen for patients with MCI according to different education levels.
MoCA-B	280 NC, 264 MCI	Cross-sectional	Chen *et al* (2016)[10]	AUC=0.90–0.95 to screen for patients with MCI according to different education levels.
	520 NC, 666 MCI	Cross-sectional	Huang *et al* (2018)[11]	AUC=0.81–0.89 to screen for patients with MCI according to different education levels.
	431 NC, 285 MCI	Cross-sectional	Pan *et al* (2022)[12]	AUC=0.90–0.95 to screen for patients with MCI according to different education levels.
ACE-III	431 NC, 285 MCI	Cross-sectional	Pan *et al* (2022)[12]	AUC=0.89–0.95 to screen for patients with MCI according to different education levels.
LASSI-L	34 MCI (Aβ+), 25 MCI (Aβ–)	Cross-sectional	Loewenstein *et al* (2018)[16]	AUC=0.77 to detect MCI with increased amyloid load.
CaST	59 MCI (Aβ+), 53 MCI (Aβ–)	Cross-sectional	Cui (2023)[17]	AUC=0.73 to detect MCI with increased amyloid load.
Metacognition assessment				
FOK and MARS	44 aMCI, 29 NC	4-year follow-up	Bastin *et al* (2021)[26]	AD converters had a higher MARS score than non-converters and controls.
JOL	105 NC	Cross-sectional	d'Oleire Uquillas *et al* (2020)[28]	Greater levels of entorhinal tau deposition were associated with overestimation of memory performance.
DOC	79 AD, 161 aMCI, 261 SCD and 196 NC	Cross-sectional	Li *et al* (2022)[29]	An increasing trend of overconfidence with the decline of cognition across the AD spectrum.
ECog	362 NC, 422 MCI and 111 dementia	Cross-sectional	Gagliardi and Vannini (2021)[30]	Increased awareness observed in the NC and decreased awareness observed in the MCI and dementia with greater amyloid burden.

Continued

Table 1 Continued

Instruments	Subjects	Type of study	Author (year)	Results
MARS	53 MCI (Aβ+), 15 NC	Cross-sectional	Antoine *et al* (2019)[32]	Low awareness was related to disconnection within the medial temporal subsystem of the default mode network.
ECog	293 MCI with intact self-awareness, 175 MCI with impaired self-awareness	24-month follow-up	Therriault *et al* (2018)[33]	MCI with impaired awareness had increased amyloid-β uptake in the posterior cingulate cortex at baseline and a nearly threefold likelihood of conversion to dementia.
ECog	360 NC, 592 MCI, 114 dementia	Longitudinally, average number of visits=4.3	Hanseeuw *et al* (2020)[34]	Awareness decreased faster in participants with increased amyloid-β burden.
Electronic assessment tools				
DCTclock	264 NC, 36 MCI/dementia	Cross-sectional	Rentz *et al* (2021)[36]	AUC=0.86 to screen for patients with MCI/dementia.
BHA	185 NC, 99 MCI (29 likely due to AD) and 42 dementia	Cross-sectional	Possin *et al* (2018)[125]	AUC=0.93 to screen for patients with MCI likely due to AD.
CBB	2866 NC and 226 MCI	Cross-sectional	Alden *et al* (2021)[38]	For discriminating all NC and MCI, AUC=0.75; for discriminating NC (A–T–) and MCI (A+T+), AUC=0.93; when differentiating MCI without AD biomarkers from those with pAD, AUC=0.86.
AMES	99 NC, 43 MCI	Cross-sectional	Huang *et al* (2023)[40]	AUC=0.88 to screen for patients with MCI.
SCS	140 NC, 80 MCI	Cross-sectional	Huang *et al* (2023)[41]	AUC=0.84 to screen for patients with MCI.

ACE-III, Third version of Addenbrooke's Cognitive Examination; AD, Alzheimer's disease; aMCI, amnestic mild cognitive impairment; AMES, Automated Memory and Executive Screening Instrument; AUC, area under the receiver operating characteristic curve; Aβ–, negative amyloid-β deposition; Aβ+, positive amyloid-β deposition; BHA, Brain Health Assessment; CaST, category switching test; CBB, Cogstate Brief Battery; DCTclock, digital clock-drawing test; DOC, degree of confidence; ECog, Everyday Cognition Scale; FOK, feeling of knowing tasks; JOL, judgements of learning; LASSI-L, Loewenstein-Acevedo Scales for Semantic Interference and Learning; MARS, Memory Awareness Rating Scale; MCI, mild cognitive impairment; MMSE, Mini Mental State Examination; MoCA-B, Montreal Cognitive Assessment Basic version; NC, cognitively normal adults; pAD, prodromal stage of AD; SCD, subjective cognitive decline; SCS, Shanghai Cognitive Screening.

cognitively normal individuals (A–T–) and MCI (A+T+) with an AUC of 0.93, and differentiate MCI participants without biomarkers from pAD with an AUC of 0.86.[38]

However, these 'Aβ+ sensitive' tests have not been applied and verified in the Chinese population. Several electronic cognitive assessment tools have already been developed to screen individuals with predementia in China.[39] For example, the Automated Memory and Executive Screening Instrument (AMES) is a self-rated screening scale that assesses individuals' abilities of memory, language and executive function. It has good convergent validity with conventional tests and is good to discriminate patients with MCI (AUC: 0.88, sensitivity: 86%, specificity: 80%) and obj-SCD (AUC: 0.78, sensitivity: 89%, specificity: 63%) from normal controls.[40]

In addition, a voice recognition-based mobile cognitive assessment tool (Shanghai Cognitive Screening, SCS) takes about 6 min to guide users to self-administrate the cognitive assessment via voice interaction, and output instant reports about their test scores and voice features using machine learning techniques.[41] Receiver operating characteristic (ROC) curve analysis showed that the SCS total score had

an AUC of 0.92 to detect AD (sensitivity=90%; specificity=95%), and an AUC of 0.84 to detect MCI (sensitivity=79%; specificity=67%). The SCS subtests demonstrated moderate to high correlations with gold standard tests and correlated positively with hippocampal volumes.

The two electronic assessment tools discussed above are either programmed on a tablet or mobile app, which are easy to administer and effective to screen for early cognitive impairment in community-based settings. However, the relationship between such instruments and amyloid-β deposition needs to be explored.

With the growing popularity of smartphones and social apps among older adults in China, the population that can be reached and the scope of screening have greatly broadened, resulting in substantial savings in human resources. As an example, a 3 min game-based cognitive assessment tool (G3, a mini-program on the WeChat platform, https://www.bestcovered.com/products) has screened more than 17 million adults online. Social media on mobile phones helps establish pilot networks of people with cognitive impairment and related risks. However, validation studies are needed to clarify the effectiveness of the above tools in detecting AD's pathology.

Notably, although electronic assessment tools have the potential to enable rapid, low-cost and large-scale screening in China, they are applicable to different scenarios. For example, G3/SCS could be used as a rapid dementia screening test on mobile devices for a community-based population, and AMES could be used as a tablet-based screening test to further classify individuals with MCI or subtle cognitive decline in primary care settings.

Some challenges also need to be tackled to ensure these digital instruments are ready for real-world application. First, the sample size of current electronic assessment tools is limited; further studies should include more participants to test their effectiveness, particularly in lower-educated and culturally diverse populations in China. Second, a quiet space and concentration on tests are required for most self-administered assessments, which may be an obstacle for at-home practice. Third, the digital divide caused by advanced age, low education and no access to or unfamiliar with electronic devices may also influence the application of these assessment tools.

Digital behavioural markers

Digital behavioural markers include physiological and behavioural information that is collected by digital techniques and quantifiable with clinical significance.[42] With the development of digital technology and medical artificial intelligence (AI), behavioural information such as eye movement,[43 44] olfactory identification,[45–47] natural speech,[41 48 49] driving[50] and gait features[51] are able to be detected via infrared, camera, recorder and wearable devices, contributing to the diagnosis and risk assessment of pAD (figure 1).

Gait

Reduced speed, extended step duration and varied trajectory are the gait characteristics associated with early AD's pathology.[52] Dual-task rather than single-task gait assessment is more recommended, during which motor and temporal parameters can be detected by wearable devices, infrared networks, cameras or gyroscopes inside mobiles

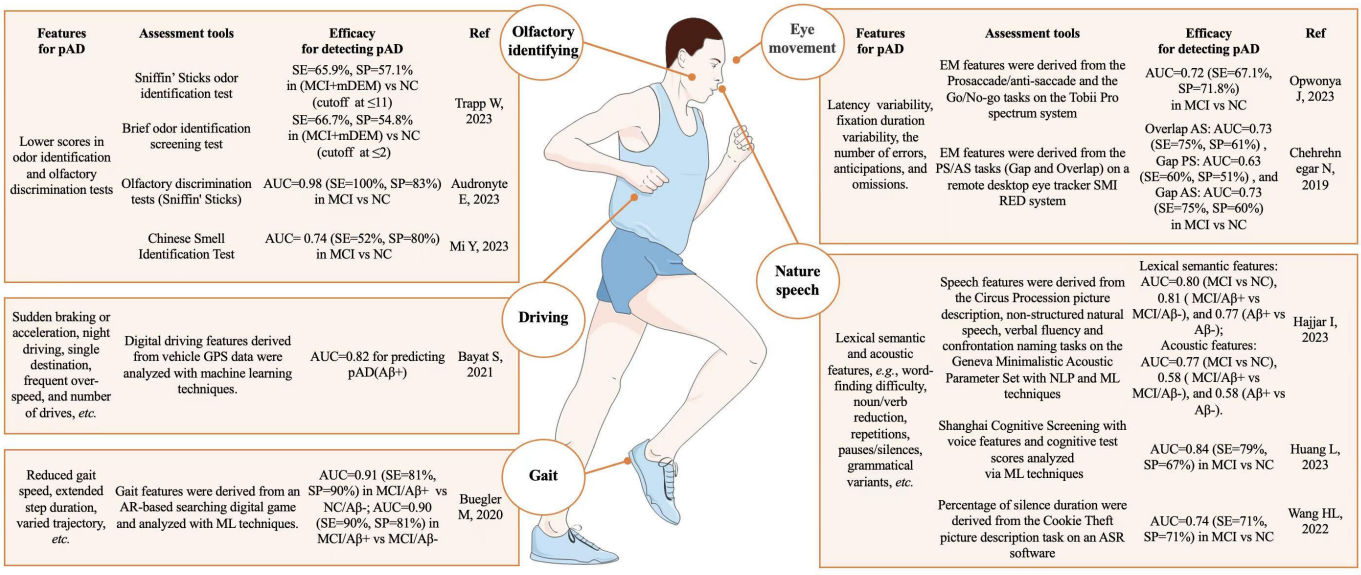

Figure 1 The digital behavioural markers for detecting prodromal Alzheimer's disease. Parts of the figure were adapted from Servier Medical Art(https://smart.servier.com/), which by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/). Aβ+, positive amyloid-β deposition; Aβ–, negative amyloid-β deposition; AR, augmented reality; ASR, automatic speech recognition; AUC, area under the receiver operating characteristic curve; EM, eye movement; GPS, Global Positioning System; MCI, mild cognitive impairment; mDEM, mild dementia; ML, machine learning; NC, cognitively normal adults; NLP, natural language processing; pAD, prodromal Alzheimer's disease; SE, sensitivity; SP, specificity.

and analysed via AI technologies.[53] An augmented reality-based digital game uses gait features (ie, step distance, speed, time length, etc) to identify cognitive impairment and predict dementia, which correlates with amyloid-PET possibility.[51]

Driving

Digital driving features derived from vehicle Global Positioning System data, such as sudden braking or acceleration, night driving, single destination, frequent overspeed and number of drives, all correlate with amyloid burden measured by PET or CSF. The model based on machine learning also had good diagnostic accuracy to predict pAD (AUC=0.82).[50]

Natural speech

Language impairment frequently occurs in pAD, including word-finding difficulty, noun/verb reduction, repetitions, pauses and silences, grammatical variants and acoustic variations. Lexical semantic (AUC=0.80) and acoustic (AUC=0.77) features distinguished MCI from cognitively normal adults. Lexical semantic provides significantly better diagnostic accuracy than acoustic, with an AUC of 0.77 to detect amyloid status and an AUC of 0.61 to screen Aβ+ cognitively normal individuals.[48]

An automatic speech recognition software for cognitive impairment takes about 2–3 min to record and analyse the percentage of silence duration (PSD) of patients' voice through a Cookie Theft picture description task to explore novel pAD screening methods. Results from the Chinese multicentre cohort found that PSD increased significantly in amnestic MCI (aMCI), with an AUC of 0.74 in the classification of aMCI and normal controls. In the Pitt centre cohort, PSD was verified as a reliable marker to differentiate mild AD from normal controls.[49]

Recommendations

1. Traditional paper-and-pencil neuropsychological tests are still the fundamental screening tools for evaluating and staging cognitive impairment (class V, level D).
2. Cognitive markers of memory binding, controlled learning and metacognition may facilitate early detection of pAD (class IIa, level B).
3. Electronic cognitive instruments show promise for the detection of underlying AD's pathology (class IIb, level B).
4. Digital behavioural markers can contribute to the massive screening of cognitive decline (class IIIa, level B).

Peripheral biomarkers

Since the current PET or CSF tests indicating AD's pathology are either expensive or invasive, we sought simple and accessible peripheral biomarkers as alternatives to identify pAD. At present, peripheral biomarkers with potential diagnostic and prognostic values are mainly derived from blood, urine and faeces. Although markers from saliva and tears have been studied, their diagnostic accuracy is far from conclusive.

Blood tests

Plasma amyloid-β (Aβ42/Aβ40) and phosphorylated tau (p-tau) are the most common blood-based biomarkers with potential clinical values. Given the relatively low levels of blood concentration, ultrasensitive methods such as single-molecule array (SIMOA), electrochemiluminescence immunoassay (ECLIA) and immunoprecipitation-mass spectrometry (IP-MS) are commonly applied for measuring plasma biomarkers.

Compared with other immunoassays, IP-MS assay showed much better accuracy and diagnostic value in measuring plasma Aβ, though numerous preanalytical steps were required.[54 55] On the other hand, the measurement of plasma p-tau was more inclined towards using automated and high-throughput immunoassays, which also displayed an excellent value in clinical applications.[56] The categorisation of various blood-based biomarkers for detecting AD is summarised in table 2.

Across different clinical cohorts, the predictive accuracy for plasma Aβ42 or Aβ42/Aβ40 ratio measured via SIMOA to detect cerebral amyloid burden determined by CSF or PET was about 59%–82%, whereas a relatively higher accuracy of 72%–97% was observed using IP-MS.[56–58] An automated diagnostic kit based on ECLIA for the quantitative determination of plasma Aβ42 and Aβ40 was first approved in Japan. Levels of plasma Aβ40 and Aβ42 measured by this assay were highly correlated with the results measured via IP-MS (r=0.91 and r=0.82), and the corresponding ratio of Aβ42/Aβ40 may effectively predict amyloid-PET with a sensitivity of 88.0% (95% CI 80.0% to 93.6%) and a specificity of 72.0% (95% CI 62.1% to 80.5%).[59]

Although the plasma Aβ42/Aβ40 ratio measured via IP-MS had high accuracy for predicting cerebral amyloid-β, the magnitude of the differences between Aβ± was only around 10%, less than the magnitude of 42% in CSF.[60 61] This low magnitude undoubtedly limits the determination of cut-offs and their clinical application. In addition, an almost complete change of plasma Aβ42/Aβ40 was observed in the asymptomatic stage, which remained relatively stable during disease progression,[62] making it difficult to detect disease progression. However, a lower level of plasma Aβ42/Aβ40 was still significantly associated with faster cognitive decline in the future.[63]

Plasma p-tau181, p-tau217 and p-tau231 are the most common p-tau proteins. In the populations with different cognitive status, plasma p-tau181 measured via SIMOA and IP-MS had an accuracy of 70%–88% and 67%–95% in discriminating brain amyloid-β positivity.[56 64–66] In addition, plasma p-tau181 is tightly associated with the progression of brain tau pathology only in the population with Aβ+.[67 68] Even in individuals without positive tau-PET, increased levels of plasma p-tau181 and p-tau217 were observed with positive amyloid-PET,[69 70] and p-tau231 was further associated with cerebral amyloid burden in cognitively unimpaired individuals.[71] These findings indicated that the levels of plasma p-tau may predate the

Table 2 Blood-based biomarker categorisation for Alzheimer's disease

Category	Markers			
Core biomarkers				
A (Amyloid)	**Aβ42**	**Aβ42/Aβ40**		
	Aβ oligomers	Aβ37	Aβ38	
T (Tau)	**P-tau181**	**P-tau217**	**P-tau231**	**P-tau205**
	P-tau199	P-tau202	MTBR-243	
Non-specific biomarkers				
N (Neurodegeneration)	**NfL**			
	T-tau	Neurogranin	SNAP25	GAP-43
	SV2A	NPTX2		
I (Inflammation)	**GFAP**			
	YKL-40	sTREM 2		

Biomarkers in bold were confirmed in blood and cerebrospinal fluid; others were established only in cerebrospinal fluid by far.
Aβ, amyloid-β; GAP, growth-associated protein; GFAP, glial fibrillar acidic protein; MTBR, microtubule binding region; NfL, neurofilament light; NPTX, neuronal pentraxin; P-tau, phosphorylated tau; SNAP, synaptosomal associated protein; sTREM, soluble triggering receptor expressed on myeloid cells; SV2A, synaptic vesicle glycoprotein 2A; T-tau, total tau; YKL-40, chitinase-3-like protein 1.

amyloid-PET examination. In contrast to plasma Aβ42/Aβ40, plasma p-tau181 showed an increasing trend and peaked at the dementia stage,[68] which assisted in monitoring disease progression. Its effectiveness in predicting conversion to AD significantly surpasses that of plasma Aβ42/Aβ40.[72]

In conclusion, plasma Aβ42/Aβ40 and plasma p-tau have potential value in screening pAD and predicting disease progression. For individuals with abnormal levels of plasma biomarkers, a clinical visit for further diagnostic tests is recommended as soon as possible. Meanwhile, using blood-based biomarkers as the first screening step may improve the efficiency of clinical trials. Though plasma biomarkers cannot currently be used as primary endpoints in clinical trials, they can be regarded as exploratory outcomes and have potential value to inform decisions. We summarised the accuracy of blood-based biomarkers for detecting brain amyloid pathology in online supplemental table S1.

Besides Aβ42/Aβ40 and p-tau, blood-based biomarkers such as neurofilament light and glial fibrillar acidic protein are also associated with AD's pathology and disease progression.[73] Lipid metabolism indicators such as oxidised low-density lipoprotein, serum inflammatory-based indicators such as advanced oxidation protein products and transforming growth factor-β, and platelet-related markers such as β-secretase all showed significant differences between cognitively normal individuals and MCI.[74] However, the relationship between these markers and AD still needs further investigation.

Urine tests

Urine samples have also been reported to contain potential biomarkers for AD, including urinary metabolites, proteins and DNA. However, available evidence is limited, and additional research is needed.

The urine formaldehyde and formic acid have been found to be correlated with global cognitive function, apolipoprotein E (APOE), plasma Aβ42 and p-tau181/t-tau and brain amyloidosis. The AUCs of urinary formic acid and formaldehyde in distinguishing normal controls from AD were 0.80 (sensitivity: 66.7%, specificity: 78.9%) and 0.57, respectively.[75 76] Using urinary formic acid and formaldehyde levels could improve the prediction accuracy for disease status.

The urinary arginine levels and global arginine bioavailability ratio (GABR) in patients with aMCI are significantly reduced and positively correlated with MMSE. ROC analysis showed that to differentiate between aMCI and normal controls, the AUC of arginine is 0.68 (sensitivity: 80.8%, specificity: 42.3%), and the AUC of GABR is 0.80 (sensitivity: 84.6%, specificity: 80.8%).[77]

The CSF levels of Alu sequence-containing cDNA of neuronal thread protein (AD7c-NTP) overexpressed in AD have been reported to be associated with the severity of dementia. A significant difference in urine AD7c-NTP has also been found between Aβ± subjects. Using 1.46 ng/mL as a cut-off, 68.8% of Aβ+ individuals showed elevated urine AD7c-NTP level, and 92.9% of Aβ− subjects showed normal urine AD7c-NTP level.[78]

Faecal tests

Clinical, in vivo and in vitro studies have shown that the brain-gut-microbiome axis plays an important role in the onset and development of AD. A large number of gut microbes and their metabolites have shown promise as novel diagnostic and therapeutic targets for AD (figure 2).

Gut microbiota diversity and alteration are associated with cognitive decline and related pathological deterioration.[79 80] It was reported that compared with normal controls, the diversity of faecal microbiota in AD was

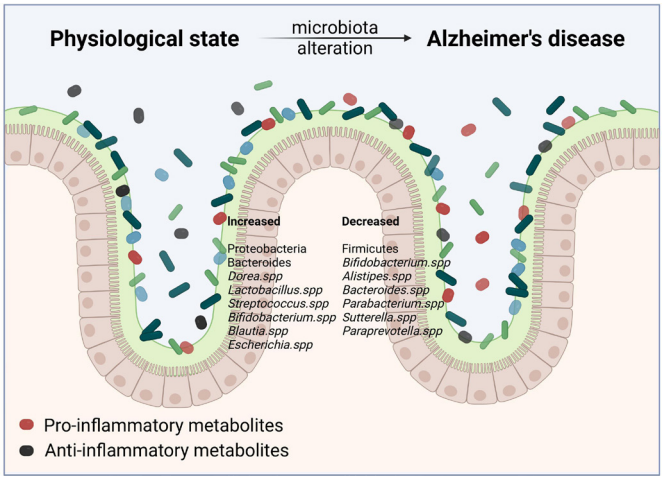

Figure 2 Gut microbiota associated with Alzheimer's disease.

reduced, along with an increase in proinflammatory and a decrease in anti-inflammatory bacteria.[81]

The proinflammatory phyla such as Proteobacteria and Bacteroides and the genera of *Dorea* spp, *Lactobacillus* spp, *Streptococcus* spp, *Bifidobacterium* spp, *Blautia* spp and *Escherichia* spp increased, whereas the anti-inflammatory phylum Firmicutes and genera *Bifidobacterium* spp, *Alistipes* spp, *Bacteroides* spp, *Parabacterium* spp, *Sutterella* spp and *Paraprevotella* spp decreased in AD.[82]

The phyla γ-Proteobacteria and Enterobacteriaceae are progressively enriched in individuals with normal cognition, aMCI and AD.[81] The abundance of some microbiota is positively correlated with cognitive scores.[83] Patients with cognitive impairment and brain amyloidosis exhibited a much lower abundance of *Eubacterium rectale* and a higher abundance of genera *Escherichia/ Shigella*.[80]

Notably, there are some inconsistent findings. For example, faecal microbes exhibited different abundances between normal control and AD, while no differential microbe was observed between MCI and AD.[84 85] There was also no significant heterogeneity between MCI and AD regarding the CSF levels of the gut microbiome-dependent metabolite,Trimethylamine-N-oxide.[85]

Additionally, animal studies provide strong evidence supporting the association between AD and gut microbiota. The divergence of gut microbiota composition between the APP/PS1 and wild-type mice was proved to start at a young age (1–3 months), before the detection of amyloid deposition, which suggested that gut bacteria alteration could aid the early detection of AD prior to pathological evidence.[86 87]

Microbial metabolites associated with AD mainly include bile acids,[88] short-chain fatty acids,[89] branched-chain amino acids, indole and pyrimidine,[90] and steroid hormones.[91] Their catabolism and synthesis are regulated by the structure and function of gut microbiota.[92] In addition, metabolites and microbes associated with chronic inflammation and immunity have also been linked to cognitive status and early brain neuropathic changes.[93] Online supplemental table S2 lists some microbial metabolites associated with AD.

Machine learning models based on microbes, metabolites and the combination of microbes and metabolites are helpful for the early diagnosis of AD.[81] Studies have shown that a series of random forest models based on 11 faecal microbe genera and their combination can distinguish cognitively normal patients and patients with MCI (considering results of MRI and PET), with the AUCs, sensitivities and specificities of 0.70–0.91, 67%–93% and 57%–93%.[85]

Faecal biomarkers for AD hold thriving prospects, yet they are still in their early phases and therefore a great deal of work needs to be done for their clinical application, including sample collection methods, measurement accuracy, interpretation of underlining mechanisms and the construction of independent or joint models.

Recommendations

1. Based on ultrasensitive methods such as SIMOA, ECLIA and IP-MS, plasma Aβ42/Aβ40 and plasma p-tau can be used to predict cerebral amyloid deposition and conversion to AD, with high sensitivity and specificity to detect pAD (class IIb, level B).
2. The popularisation of blood-based biomarkers depends on the standardisation of data from different laboratories (class V, level D).
3. Urinary formic acid, GABR and AD7c-NTP can help predict cerebral amyloid deposition (class IIIb, level B).
4. Models based on multiple microorganisms, metabolites and combinations of microorganisms and metabolites contribute to the early diagnosis of pAD (class IIIb, level B).

Brain imaging

Neuroimaging and electrophysiological examinations can effectively inform the diagnosis of pAD. Although PET imaging is not yet sufficient for rapid screening, a variety of other techniques have also shown promise in this field.

MRI

According to the 2018 NIA-AA biological framework,[94] biomarkers in the (N) group indicate neurodegeneration and are usually tested by MRI. Although 'N' biomarkers are not specific to AD's pathology, the use of MRI still plays an important role in several aspects: (1) excluding cognitive impairment caused by other diseases; (2) combined with other AD biomarkers to predict disease progression[95]; and (3) clinical staging and differential diagnosis.[94]

Structural MRI is one of the most important methods to detect pAD, which can detect structural brain changes 10 years before clinical cognitive decline in AD. Hippocampal volume can be regarded as an indicator to evaluate the pathological change caused by AD.[96] The visual assessment scale of medial temporal lobe atrophy (MTA

scale) is concise and commonly used, but it is not sensitive enough for younger patients with pAD and may lead to false negatives.

Both hippocampal volume and hippocampal texture provide valuable information for predicting the conversion from MCI to AD.[97 98] The asymmetry of bilateral hippocampal atrophy, in which the right hippocampus is more atrophic than the left hippocampus, may also help in the early detection of AD. A systematic review showed that the volume of overall hippocampi could identify MCI with a sensitivity of 73% and a specificity of 71%; MTA with a sensitivity of 64% and a specificity of 65%; and lateral ventricles with a sensitivity of 57% and a specificity of 64%.[99] Analysis of hippocampus evolution patterns increases the accuracy to 91.76% for conversion prediction.[100]

However, the screening value of other brain regions such as the entorhinal cortex, whole brain volume, lateral temporal lobe, amygdala, medial temporal gyrus or grey matter volume varied across studies. In Aβ+ patients with MCI, MTA and posterior atrophy were associated with an increased risk for progression to dementia, including the posterior cingulate sulcus, precuneus, parieto-occipital sulcus and parietal lobes.[101–103] Furthermore, smaller medial temporal lobes were found in SCD subjects with abnormal CSF Aβ42.[104]

The atrophy of hippocampal subfields has a potential value in the differential diagnosis of AD.[105] Atrophy in the insula, amygdala, precuneus, hippocampus and other temporal regions occurred before the clinical threshold for CSF amyloid positivity,[106] and an automated classifier based on clinical, imaging and APOE can identify the presence of amyloidosis with a moderate level of accuracy.[107]

Longitudinal brain volumetric changes can also predict the presence of amyloid abnormalities and can avoid 55% unnecessary CSF or PET scans.[108] Using radiomics models from MRI can help predict amyloid positivity in patients with MCI.[109] We summarised the structural MRI regions associated with pAD in table 3.

Some other MRI technologies, such as resting-state functional MRI and diffusion tensor imaging, as well as novel AI-based approaches, such as machine learning and convolutional networks, have improved the accuracy of MRI for the diagnosis of pAD.[106 110–113] Multiscale graph-based grading of anatomical structures can accurately predict the conversion of MCI to AD.[114] Although these methods lack practicality for simple screening purposes, they deserve continuous attention and further research.

Retinal imaging techniques

The retina shares the same embryological origin and physiological characteristics as the central nervous system and is structurally and functionally associated with the brain. As the only part of the central nervous system that can be directly visualised, biomarkers of retina imaging allow potential non-invasive assessments of pAD.

Recent advancements in retinal imaging techniques include the following: (1) optical coherence tomography (OCT), which provides measurement of the thickness of the retinal nerve fibre layer (RNFL) and ganglion cell-inner plexiform layer (GCIPL). The deposition of amyloid-β in the eye of patients with AD causes loss of ganglion cells and their axons, which ultimately leads to optic nerve degeneration and the thinning of RNFL and GCIPL[115]; (2) OCT angiography, which provides high-resolution images of the choroidal microvasculature to visualise the gradual changes in retinal blood vessels[116]; (3) electrophysiological examination of the retina, such as the electroretinogram; and (4) other new retinal imaging technologies for detecting amyloid deposition, such as retinal hyperspectral imaging and adaptive optics scanning laser ophthalmoscopy.[117]

Electrophysiological examination

Scalp electroencephalogram (electroencephalograph, EEG) records the sum of the postsynaptic potential generated by the pyramidal cells of the cerebral cortex, which can reflect the synaptic function of the brain. EEG is an economical, convenient and non-invasive screening method that can be used as a marker for pAD. Resting-state EEG, event-related potentials (ERP) and sleep EEG are the main EEG screening modules.

Resting-state EEG

Spectral analysis studies the EEG in terms of its dominant frequency, power (or amplitude), phase and synchrony of the EEG rhythm. Resting-state eye-closed EEG rhythms often change with physiological ageing. In the resting state, the EEG power density spectrum (power spectrum density) of healthy older individuals, MCI and AD showed differences in distribution and frequency.

Increased delta or theta power density, decreased alpha and beta power density and slowed mean EEG frequency have been shown to predict the progression from MCI to dementia. The alpha rhythm of high-power density in the back of the head also predicts more stable cognitive function in MCI subjects.[118] In patients with MCI, increased power density of theta and delta rhythms and decreased power density of beta rhythms in temporal and occipital regions may indicate disease progression.[119] As neurodegeneration develops, abnormalities in brain network connections that affect cognitive function develop.

The ideal approach would be to extract some indicators of functional brain connectivity abnormalities in neural networks to reveal such changes in cognitive function. Measurement of the functional coupling of rhythms between pairs of resting-state EEG electrodes with eyes closed is a promising marker of functional neural connectivity. Therefore, spectral analysis and 'interrelatedness' resting-state EEG measures (eg, directed transfer function, phase lag index, linear lagged connectivity, etc) at delta, theta and alpha frequency bands may be useful for stratification

Table 3 Brain regions associated with prodromal Alzheimer's disease

Regions	Subjects	Targets	Standards	Accuracy	References
Core regions					
MTL	Total: 1077 (SR)	Identify MCI	Follow-up	SE: 64%, SP: 65%	Lombardi *et al*[99]
	NC: 79, Pre-AD: 50, MCI/AD: 274	Identify amyloid-β pathology	Follow-up, CSF	AUC: 0.87	Petrone *et al*[108]
	MCI: 258	MCI conversion	Follow-up 3 years, PET/CSF	HR:1.682 to AD	Pyun *et al*[101]
Hippocampus	NC: 90, MCI: 145	MCI conversion	Follow-up 1–2 years	Conversion prediction: 91.76%	Zhang *et al*[113]
	NC: 213, MCI: 216, AD: 130	MCI conversion	Follow-up 3 years	AUC (MRI): 0.81, AUC (MRI+cognition): 0.85	Hett *et al*[114]
	MCI: 407	Identify amyloid-β pathology	CSF	AUC (radiomics analysis): 0.67, AUC (combined model): 0.82	Park *et al*[109]
	Total: 2209 (SR)	Identify MCI	Follow-up	SE: 73%, SP: 71%	Lombardi *et al*[99]
	NC: 121, mild AD: 145, MCI: 194	MCI conversion	Follow-up ≥2 years	AUC (texture): 0.79, AUC (composite): 0.81, AUC (volume): 0.74	Lee *et al*[97]
	MCI: 295	MCI conversion	Follow-up 5 years	Larger volume associated with 45% and 81% lower risk of conversion from MCI to AD	Tabatabaei-Jafari *et al*[98]
	NC: 305, obj-SCD: 153, MCI: 289	Differences between amyloid-β±	Follow-up, PET	A+ had lower volume of the presubiculum (3.4% smaller)	Thomas *et al*[102]
	NC: 337, MCI: 375, AD: 98	Identify amyloid-β pathology	Follow-up, PET/CSF	AUC (MCI): 0.81, AUC (NC): 0.74	Ten Kate *et al*[107]
Entorhinal cortex	NC: 60, SCD: 60, MCI: 80	MCI conversion to AD	Follow-up ≥1 year, PET/CSF	AUC: 0.70 (SE: 53%, SP: 86%)	Traschütz *et al*[103]
	NC: 305, obj-SCD: 153, MCI: 289	Obj-SCD and MCI outcomes	Follow-up 4 years and PET	Obj-SCD (r=−0.126) and MCI (r=−0.261) had faster entorhinal cortex thinning	Thomas *et al*[102]
Non-core regions					
Lateral ventricles	Total: 1077 (SR)	Identify MCI	Follow-up	SE: 57%, SP: 64%	Lombardi *et al*[99]
Posterior cortex	MCI: 258	MCI conversion	Follow-up 3 years, PET/CSF	HR: 2.244 (1.497–3.364)	Pyun *et al*[101]

AD, Alzheimer's disease; AUC, area under the receiver operating characteristic curve; CSF, cerebrospinal fluid; HR, hazard ratio; MCI, mild cognitive impairment; MTL, medial temporal lobe; NC, cognitively normal adults; obj-SCD, objectively defined subtle cognitive decline; PET, positron emission tomography; SCD, subjective cognitive decline; SE, sensitivity; SP, specificity; SR, system review.

of AD and monitoring of disease progression and intervention.[120]

Event-related potential

ERP is brain electricity extracted from spontaneous potentials, known as evoked potentials. ERP can directly express the electrical response of the cerebral cortex to sensory, emotional or cognitive events.[121] In the process of ERP research, researchers have made a finer division of ERP components, including ERP component polarity, cortical source location, amplitude and latency. Online supplemental figure S1 shows the waveforms and latencies of common ERP components. The ERP indicators related to early recognition of cognitive decline are listed in online supplemental table S3.

Sleeping EEG

Approximately two-thirds of patients with MCI subjectively report sleep-wake disturbances.[122] Sleep monitoring using nocturnal polysomnography revealed abnormalities in the macrostructure of sleep in MCI relative to age-matched controls: prolonged sleep onset, delayed rapid eye movement (REM) sleep onset and decreased duration

of REM and slow-wave sleep.[123] Studies have shown lower overall δ in non-REM (NREM) sleep and lower overall power in both NREM and REM sleep in aMCI compared with controls.[124] Pathological changes in NREM and REM sleep may predict the trajectory of cognitive decline in older adults.

The advantages of neuroimaging techniques, electrophysiological examinations and retinal imaging technologies lie in their relatively low cost, rapidity and non-invasiveness to allow massive screening in the context of large-scale screening applications, but their current applications are still limited due to a lack of validation studies with biomarker evidence.

Recommendations

1. T1-weighted MRI is a feasible and reliable imaging method for screening pAD. The atrophy in some brain areas (eg, hippocampus, amygdala, precuneus, temporal lobe) is sensitive to amyloid pathology (class IIb, level B).
2. Non-invasive retinal examinations (eg, OCT) have potential value for screening pAD (class IIIb; level B).
3. Brain electrophysiology examination is relatively cheap and easy to conduct, and can be employed as ancillary diagnostic tests for detecting early cognitive decline, yet their predictive value still needs more research (class IIIb, level B).

SCREENING PROCESS FOR pAD

In conclusion, we recommend the following three steps to screen for pAD (figure 3):

Step 1: A preliminary screening should be carried out in the community or primary care settings using brief screening scales. Individuals who are suspected to have cognitive impairment are then transferred to specialised outpatient clinics for further examination, including systemic medical history collection, physical examination, laboratory testing and brain imaging. After the initial procedures described above, individuals can be categorised into one of three groups: cognitively normal, dementia and transitional stage. Cognitively normal adults should be followed up. Patients with dementia should be given standardised treatment.

Step 2: Individuals in the transitional stage should proceed to further screening, including 'Aβ+ sensitive' cognitive tests, blood biomarkers and brain atrophy evaluation. Individuals with impaired scores on 'Aβ+ sensitive' tests (such as CaST and metamemory), abnormal blood biomarkers (decreased plasma Aβ42/Aβ40 and increased p-tau181) and brain atrophy in the hippocampus, amygdala, precuneus or temporal lobe should be assigned the label of 'high-risk pAD' and proceed to step 3 for further examination. Patients who are suspected of having other diseases (eg, cognitive impairment caused by vascular dementia or Parkinson's disease) should be

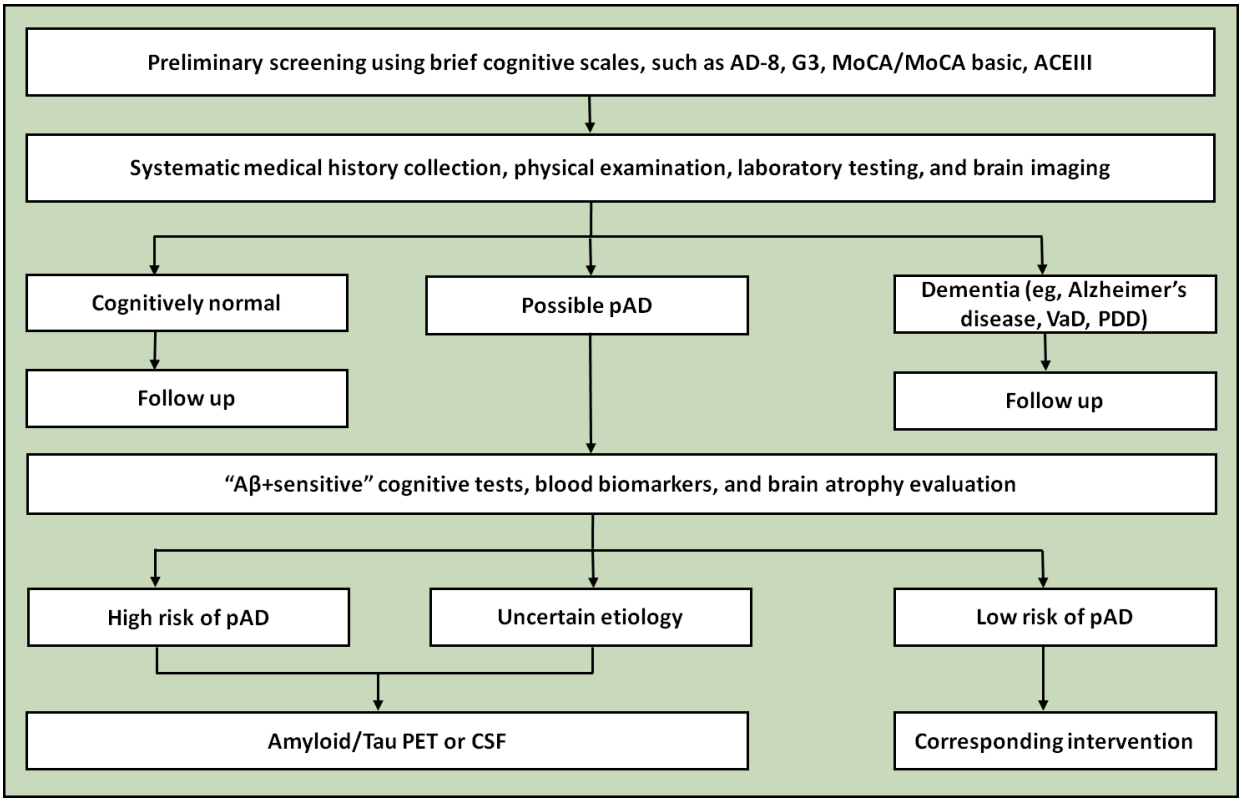

Figure 3 Workflow for screening prodromal Alzheimer's disease. Aβ+, positive amyloid-β deposition; ACEIII, Third version of Addenbrooke's Cognitive Examination; AD-8, Ascertain Dementia 8-item Questionnaire; CSF, cerebrospinal fluid; G3, 3 min version of game-based cognitive assessment; MoCA, Montreal Cognitive Assessment; pAD, prodromal Alzheimer's disease; PDD, Parkinson's disease dementia; PET, positron emission tomography; VaD, vascular dementia.

given appropriate interventions. Those with no identifiable cause (uncertain aetiology) should proceed to step 3.

Step 3: If the individual is still undiagnosed after all the above examinations, a PET scan or CSF testing should be performed for a definite diagnosis.

CONCLUSION AND FUTURE DIRECTIONS

This consensus provides a series of non-invasive, low-cost and easy-to-use approaches for the rapid screening of pAD. The current literature review shows promising evidence that advances in 'Aβ+ sensitive' cognitive tests, novel blood biomarkers and MRI techniques are potential measurements of AD's pathology. The application value of more advanced technologies, such as digital markers, urine and faecal tests and non-invasive retinal imaging, needs to be further explored. Since blood tests are cheaper and less invasive than PET/CSF, they might be the first step in the screening process for pAD in the near future. However, current peripheral biomarkers are tested in different laboratories using varied methods and measurement standards in China, which can impact the comparability and accuracy of screening. Therefore, establishing standardised testing methods and procedures to facilitate future advancements in precision medicine is of great importance.

Future research should include further validation of new screening methods (including strengths and limitations), improvements to existing methods and further large-scale studies to validate the efficacy of pAD screening tools. Moreover, if a vaccine for AD becomes available in the future, interventions should focus on the cognitively impaired individuals and on those with normal cognition underlying AD's pathology. We believe that before novel markers become reliable screening methods, it is necessary to confirm that they are related to AD's pathology. Having such screening methods available will greatly increase diagnostic accuracy in clinical trials and can be promoted in memory clinics or primary care settings. This expert consensus is proposing pAD screening methods for China's current state of affairs and offering insights for the screening of cognitive disorders in low-income regions worldwide.

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Acknowledgements This consensus obtained advice from 32 experts apart from the 13 authors. We appreciate the contributions of Xinyi Cao, Yunpeng Cao, Qin Chen, Yan Zeng, Yifeng Du, Ying Han, Chuzhong Huang, Binyin Li, Fang Li, Xia Li, Yunxia Li, Wenlin Ma, Dantao Peng, Guoping Peng, Yanghua Tian, Jianjun Jia, Jiong Shi, Yi Tang, Huali Wang, Gang Wang, Yanjiang Wang, Fang Xie, Jun Xiao, Qun Xu, Jiewen Zhang, Min Zhang, Nan Zhang, Wei Zhang, Yu Yang, Jintai Yu, Junjian Zhang and Qianhua Zhao. Parts of this consensus have been published in the *Chinese Journal of Neuromedicine* previously.

Contributors XC, JJ and QG designed and initiated the consensus. LH, QL, YLu, FP, LC, YW, YM, TC, YLi and JW carried out the literature review. LH drafted the manuscript. XC, JJ and QG critically reviewed the manuscript. QG served as the guarantor of this study. All authors read and approved the final manuscript.

Funding This work was supported by the National Natural Science Foundation of China (82171198, U20A20354) and the Sci-Tech Innovation 2030 Agenda of China (2022ZD0211603).

Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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Supplementary Materials

Table S1. Accuracy of blood-based biomarkers for detecting brain amyloid pathology.

Biomarkers	Method	Subjects	Standard	AUC (Aβ+/Aβ-)	References
Aβ42	SIMOA	274 NC, 174 SCD, 214 MCI, 57 AD	CSF	0.65	Janelidze et al. 2016 [1]
	SIMOA	248 SCD	CSF, PET	CSF: 0.66; PET: 0.66	Verberk et al. 2018 [2]
	SIMOA	276 SMC	PET	0.68	Vergallo et al. 2019 [3]
	SIMOA	441 non-dementia	PET	0.59	Keshavan et al. 2021 [4]
	SIMOA	238 NC, 118 SCD, 135 MCI, 118 Dementia	PET	0.59	Pan et al. 2023 [5]
	IP-MS	218 NC, 97 MCI, 58 AD	PET	Cohort 1: 0.87 Cohort 2: 0.72	Nakamura et al. 2018 [6]
Aβ42/40	SIMOA	441 non-dementia	PET	0.62	Keshavan et al. 2021 [4]
	SIMOA	14 NC, 30 CIND, 9 VaD, 15 AD	PET	0.82	Tanaka et al. 2021 [7]
	SIMOA	182 NC, 104 MCI	CSF, PET	CSF: 0.69; PET: 0.65	Janelidze et al. 2021 [8]
	SIMOA	248 SCD	CSF, PET	CSF: 0.77; PET: 0.68	Verberk et al. 2018 [2]
	SIMOA	161 NC, 38 MCI	PET	0.79	De Meyer et al. 2020 [9]
	SIMOA	276 SMC	PET	0.79	Vergallo et al. 2019 [3]
	SIMOA	274 NC, 174 SCD, 214 MCI, 57 AD	CSF	0.68	Janelidze et al. 2016 [1]
	SIMOA	238 NC, 118 SCD, 135 MCI, 118 Dementia	PET	0.65	Pan et al. 2023 [5]
	IP-MS	182 NC, 104 MCI	CSF, PET	CSF: 0.85; PET: 0.83	Janelidze et al. 2021 [8]
	IP-MS	218 NC, 97 MCI, 58 AD	PET	Cohort 1: 0.97 Cohort 2: 0.84	Nakamura et al. 2018 [10]
	IP-MS	158 NC	PET	0.88	Schindler et al. 2019 [11]
P-tau181	SIMOA	441 non-dementia	PET	0.70	Keshavan et al. 2021 [4]
	SIMOA	400 NC, 558 MCI, 219 AD	PET	0.77	Karikari et al. 2021 [12]
	SIMOA	113 NC, 45 MCI,	PET	0.88	Karikari et al. 2020 [13]

		33 AD, 8 non-AD, 27 young adult			
	SIMOA	69 NC, 47 MCI, 56 AD, 190 non-AD	PET	0.91	Thijssen et al. 2020 [14]
	SIMOA	238 NC, 118 SCD, 135 MCI, 118 Dementia	PET	0.70	Pan et al. 2023 [5]
	MSD	172 NC, 57 MCI, 40 AD	PET	0.80	Mielke et al. 2018 [15]
	MSD	219 NC, 125 MCI,	PET	0.81	Janelidze et al. 2020 [16]
	IP-MS	73 NC, 45 MCI, 8 AD	PET	Cohort 1: 0.95 Cohort 2: 0.72	Barthelemy et al. 2020 [17]
P-tau217	MSD	301 NC, 178 MCI, 121 AD, 99 non-AD	PET	0.87	Palmqvist et al. 2020 [18]
P-tau231	SIMOA	159 NC, 54 MCI	PET	NC: 0.83; MCI: 0.80	Ashton et al. 2021 [19]

Note: Aβ+ = amyloid-β positive; Aβ- = amyloid-β negative; AD, Alzheimer's disease; AUC, area under the receiver operating characteristic curves; CIND, cognitive impairment - no dementia; CSF, cerebrospinal fluid; IP-MS, Immunoprecipitation followed by mass spectrometry; MCI, mild cognitive impairment; MSD, Meso Scale Discovery; NC, cognitively normal adults; PET, positron emission tomography; SCD, subjective cognitive decline; SIMOA, single molecule array; SMC, subjective memory complaint; VaD, vascular dementia.

Table S2. Microbial metabolites associated with AD.

Biomarkers	Male	Female	References
Bile acid	NC versus AD: T-β-muricholic acid↓	NC versus AD: glycoursodeoxycholic acid, glycodeoxycholic acid, α-muricholic acid, β-muricholic acid, and ω-muricholic acid↑	Wu et al. 2020 [20]
	NC versus AD: lithocholic acid↓		
Short chain fatty acid	MCI versus AD: formic acid, acetic acid, propanoic acid, 2-methylbutyric acid, and isovaleric acid↓		Wu et al. 2021 [21]
	NC versus MCI or AD: formic acid, acetic acid, propanoic acid, 2-methylbutyric acid, Butyric acid, Isovaleric acid, Valeric acid↓		
Neurotransmitter	NC versus AD: serotonin, 5-methoxytryptophan, indole derivatives↓; indole-3-pyruvic acid↑		Wu et al. 2021 [21]
Steroid	NC versus AD: 19-Oxoandrost-4-ene-3,17-dione, 1α,25-vitamin D3↓; Trigofoenoside F, Angeloylbarringtogenol C, Sagittariol↑		Tynkkynen et al. 2018 [22]

Note: ↑ = increased in MCI and/or AD compared to control group; ↓ = Decreased in MCI and/or AD compared to control group.

Abbreviations: AD = Alzheimer's disease, MCI = mild cognitive impairment, NC = cognitively normal adults.

Table S3. Comparison of effectiveness of ERP components in differentiating cognitive decline stages.

ERP components	**Comparison**	**Sensitivity**	**Specificity**	**References**
P50 amplitude	MCI versus AD	81%	77%	Kozlowska et al. 2016 [23]
P200 latency	Progressive MCI versus stable MCI	88%	77%	Lijffijt et al. 2009 [24]
N2b latency	Progressive MCI versus stable MCI	75%	69%	Missonnier et al. 2007 [25]
N2b latency	NC versus mdaMCI	83%	81%	Fernandez et al. 2013 [26]
N2pc latency	NC versus mdaMCI	92%	84%	Cespón et al. 2015 [27]
P3b latency	NC versus MCI	80%	100%	Cespón et al. 2015 [28]
N400 amplitude	NC versus AD	55%	91%	Parra et al. 2012 [29]

Abbreviations: AD = Alzheimer's disease, ERP = Event Related Potential, MCI = mild cognitive impairment, mdaMCI = multiple-domain amnestic MCI, NC = cognitively normal adults.

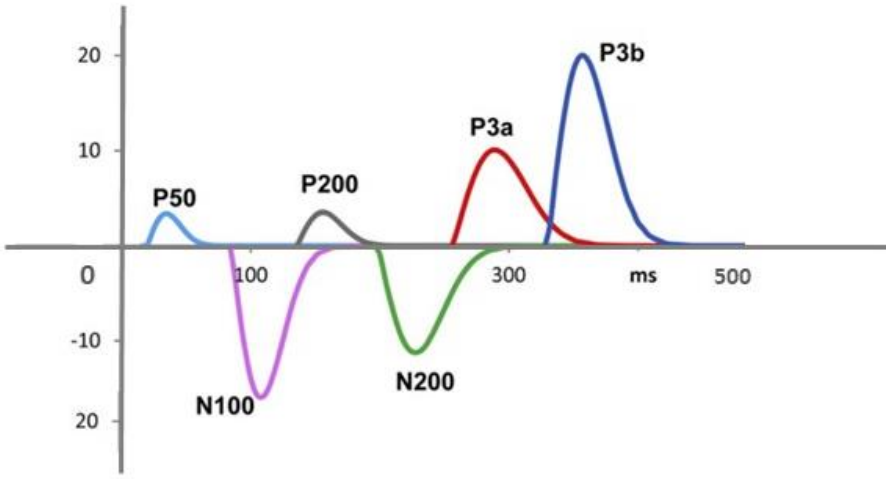

Figure S1. Diagram of Event Related Potential (ERP) Components.
The waveforms and latencies of common ERP components related to early recognition of cognitive decline.

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