Strategic roadmap for an early diagnosis of Alzheimer's disease based on biomarkers

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The diagnosis of Alzheimer's disease can be improved by the use of biological measures. Biomarkers of functional impairment, neuronal loss, and protein deposition that can be assessed by neuroimaging (ie, MRI and PET) or CSF analysis are increasingly being used to diagnose Alzheimer's disease in research studies and specialist clinical settings. However, the validation of the clinical usefulness of these biomarkers is incomplete, and that is hampering reimbursement for these tests by health insurance providers, their widespread clinical implementation, and improvements in quality of health care. We have developed a strategic five-phase roadmap to foster the clinical validation of biomarkers in Alzheimer's disease, adapted from the approach for cancer biomarkers. Sufficient evidence of analytical validity (phase 1 of a structured framework adapted from oncology) is available for all biomarkers, but their clinical validity (phases 2 and 3) and clinical utility (phases 4 and 5) are incomplete. To complete these phases, research priorities include the standardisation of the readout of these assays and thresholds for normality, the evaluation of their performance in detecting early disease, the development of diagnostic algorithms comprising combinations of biomarkers, and the development of clinical guidelines for the use of biomarkers in qualified memory clinics.

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Introduction

In the past decade, the definitions of Alzheimer's disease dementia (panel 1) and other forms of dementia used by researchers have changed. Instead of using a traditional approach based on clinical presentation and findings obtained at autopsy, investigators now base diagnoses on biological measures (that is, biomarkers) specific for each of these neurological diseases.

Different biomarkers (panel 1, table 1) are now used by researchers in their diagnostic criteria,[8,9] Although research criteria are not supposed to be used in clinical settings, many academic memory clinics use these biomarkers in routine practice to help assessment and management of patients. Without a consistent framework to assess the validity of biomarkers for Alzheimer's disease, however, their use has been heterogeneous and reimbursement by providers of health insurance inconsistent. Both factors are negatively affecting the provision of high-quality care to patients because the informative value of biomarkers cannot be used with full reliability in clinical practice.

In this Policy View, we summarise the conclusions and recommendations from an interdisciplinary academic effort to set up a strategic research agenda (or roadmap, panel 1) to accelerate the adoption of biomarkers for the diagnosis of Alzheimer's disease in clinical practice. Our strategic roadmap is rooted in a framework for validation of biomarkers previously used in oncology. We focus on biomarkers that can help in the differential diagnosis of mild cognitive impairment, the stage that precedes Alzheimer's disease (panel 1) and the clinical condition with the greatest diagnostic uncertainty that would benefit most from accurate diagnosis.

We outline the clinical context for the need of Alzheimer's disease biomarkers, discuss the development and validation of these biomarkers, present a structured framework for Alzheimer's disease biomarker development, and propose the research priorities required for its validation.

The need for biomarkers

In 1906, Alois Alzheimer[10] defined the disease that was later to carry his name as a condition that involves progressive cognitive impairment and behavioural changes underpinned by senile plaques and neurofibrillary tangles identified post mortem in the grey matter of the brain. Decades later, the plaques and neurofibrillary tangles were found to be composed of β-amyloid and hyperphosphorylated tau (p-tau) protein, respectively,[11,12] and the clinical symptoms were shown to correlate with synaptic and neuronal loss.[13,14] The first criteria from the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association for the diagnosis of Alzheimer's disease were developed in 1984,[1] when biomarker development for this disorder was in its infancy. Diagnosis at that time was based on clinical findings exclusively, with measurement of biomarkers, especially brain imaging biomarkers, recommended only to exclude other causes of cognitive decline.

In the following decades, substantial technological advances in neuroimaging (MRI and PET) and CSF analysis allowed the development of biomarkers related to neurodegeneration, cerebral β-amyloid deposition, and tau-related pathology (table 1). Extensive evidence of

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***Panel 1*: Glossary of terms**

Alzheimer's disease dementia
Traditionally, and according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria, Alzheimer's disease was defined as a syndrome with progressive cognitive impairment severe enough to affect daily activities. A diagnosis of Alzheimer's disease can be made only after exclusion of other possible causes of cognitive impairment.[1] 65–80% of patients who fulfil these criteria have Alzheimer's pathology in their brain (plaques and tangles), with the remainder having various other pathologies. To increase diagnostic certainty, research criteria for Alzheimer's disease dementia incorporate biomarker evidence for pathology, which can be obtained by neuroimaging (MRI measures of atrophy, ^{18}F-fluorodeoxyglucose PET measures of cerebral hypometabolism, and amyloid PET measures of β-amyloid deposition) and CSF testing (decreased β-amyloid concentrations or increased total tau and hyperphosphorylated tau concentrations).[2,3]

Alzheimer's pathology
The hallmarks of disease detected in the brains of patients at autopsy are plaques, mainly comprising β-amyloid deposits outside neurons, and neurofibrillary tangles, which consist mainly of hyperphosphorylated tau deposits inside neurons and, usually, although not invariably, are co-localised with neuronal and synaptic loss. Pathology is the gold standard for diagnosis. Amyloid PET is an accurate in-vivo proxy for moderate to frequent plaques. Alzheimer's disease pathology begins many years before symptoms emerge and, therefore, the disease process spans a continuum from asymptomatic to prodromal stages, and finally to the dementia stage;[4] Individuals at the asymptomatic stage can only be identified by biomarkers of Alzheimer's pathology, but whether biomarkers in the asymptomatic stage can predict clinical symptoms in the future remains unclear.

Biomarker
An objectively measurable substance, characteristic, or other parameter of a biological process that enables assessment of disease risk or prognosis and provides guidance for diagnosis or monitoring of treatment. Biomarkers are developed and validated through the process of analytical validation, clinical validation, and the demonstration of clinical utility.

Mild cognitive impairment
A syndrome of acquired cognitive impairment without functional limitation that has heterogeneous presentations and underlying pathologies; up to two-thirds of patients with amnestic mild cognitive impairment have underlying Alzheimer's pathology (these individuals are also considered to be at the prodromal Alzheimer's disease stage), 15–25% have neurodegenerative diseases other than Alzheimer's disease (eg, hippocampal sclerosis, frontotemporal degeneration, or Lewy body disease), and the remainder have normal age-related changes[5–7]

Prodromal Alzheimer's disease
Alzheimer's disease stage after symptoms have begun to manifest but before disability is apparent (ie, during the mild cognitive impairment stage)

Roadmap
An objective-oriented, structured, and efficient action plan that can also be considered a strategic research agenda.

analytical and early clinical validity for these biomarkers led to them being integrated into research diagnostic criteria, with the aim of moving from an exclusionary approach in differential diagnosis to a positive diagnosis.[2,3,8,15] Changes in biomarkers can already be seen in the mild cognitive impairment stage, when functional disability is absent,[9] and new diagnostic criteria now allow for a diagnosis of Alzheimer's disease to be made at the prodromal stage, before the development of full-blown dementia (panel 2).[2,8,15,16] Biomarkers can also be used in the full-blown dementia stage to improve the accuracy of the diagnosis,[20,21] and, potentially, as a screening tool in the general population to identify people at high risk of developing dementia.[16,22]

Challenges of biomarker development and implementation in Alzheimer's disease

Clinical needs, scientific and technical advances, the regulatory milieu, and commercial opportunities determine the use of diagnostic biomarkers for Alzheimer's disease in clinical practice. The challenges posed by these factors are discussed in this section.

Diagnostic pressure leads to development of local tests

Patients' expectations of increasingly accurate diagnoses, together with the existence of little incentive for pharmaceutical companies to engage in the lengthy and complex procedures for biomarker development, validation, regulatory approval, and reimbursement, stimulate the local development of different tests and cutoff values in different laboratories.[23] For example, many different procedures are used to assess hippocampal volume[24] and cortical hypometabolism.[25,26] Efforts have been made to achieve standardisation, but, with a few notable exceptions,[27,28] they fall short of approval for clinical use by regulatory agencies. Nevertheless, these tests are often used to guide diagnosis and treatment of symptoms in clinical settings under the responsibility of local clinicians.[29,30]

Clinical use before regulatory approval

The promise of Alzheimer's disease biomarkers to enable earlier and more precise diagnosis than the traditional clinical assessment leads clinicians to use them even without regulatory approval. Since diagnosis is at stake rather than treatment, an underlying assumption seems

to be that the margin of error is not linked to potential harm to patients. However, the use of a diagnostic test with poor performance or insufficient validity can have important implications: poor sensitivity (leading to false-negative diagnoses) might result in patients being given false reassurance and excluded from appropriate treatments or access to clinical trials; poor specificity (leading to false-positive diagnoses) can result in over-diagnosis, causing unnecessary anxiety, overtreatment, and inappropriate inclusion in clinical trials, which could expose patients to unnecessary side-effects and dilute potential treatment effects.[31] Physicians should, therefore, be fully aware of the clinical and ethical implications of the pre-regulatory use of biomarkers.

Validation of some diagnostic tests is incomplete

Efforts to standardise and validate biomarkers have varied. Some biomarkers are the subject of one or more initiatives aimed at standardisation or utility analysis, but others are less well investigated. For example, despite ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET being widely regarded as a useful biomarker for the early detection of Alzheimer's disease,[32,33] there is no structured programme aimed at standardising the readout of cortical hypometabolism measured in this way.

The systematic assessment of Alzheimer's disease biomarkers in representative populations is particularly relevant to their implementation in routine clinical practice. Indeed, the highly selected patients included in the assessment of biomarkers in the initial phases of their development might not be representative of real-world populations (eg, with regard to comorbidities, socioeconomic status, or education), such that biomarkers might yield notably different results in research settings from those in clinical settings.[34] No data are yet available on changes in health outcomes (disability, mortality, morbidity, or quality of life) attributable to the use of Alzheimer's disease biomarkers, which is due partly to the lack of treatments able to delay disease progression, access to which is likely to depend on fulfilment of biomarker-supported criteria. Biomarker validation is further hampered by the lack of a consistent methodological framework.

Synergies are poor among research initiatives addressing biomarker standardisation

Several Alzheimer's disease biomarker validation programmes have been launched. The Alzheimer's Association leads several of these biomarker standardisation initiatives, including the External Quality Control Program for CSF Biomarkers,[35] and has sponsored the European Alzheimer's Disease Consortium and Alzheimer's Disease Neuroimaging Initiative Harmonized Protocol for Manual Hippocampal Segmentation on Magnetic Resonance (HarP).[36] The Joint Programming Neurodegenerative Diseases of the European Commission has funded BiomarkAPD,[37] which has similar aims to those of the External Quality Control Program for CSF Biomarkers. The Radiological Society of North America has launched the Quantitative Imaging Biomarkers Alliance to unite researchers, health-care professionals, and the industry to advance quantitative imaging and the use of imaging biomarkers in clinical trials and clinical practice. For amyloid imaging, the Alzheimer's Association leads the US Imaging Dementia—Evidence for Amyloid Scanning (IDEAS) study (NCT02420756), with management by the American College of Radiology Imaging Network. In Europe, the European Commission and European Federation of Pharmaceutical Industries and Associations have funded the Amyloid imaging to Prevent Alzheimer's Disease (AMYPAD).

Although these initiatives address important issues related to biomarker standardisation, clinical utility, or both, each focuses on one biomarker or class of biomarkers. In the absence of a common framework, it is not straightforward for synergies to be exploited or to harness collaborative efforts.

Slow translation of biomarker research into clinical practice

Despite the huge amount of reported evidence from single-centre and multicentre trials and meta-analyses that support the use of biomarkers for the diagnosis of Alzheimer's disease, their uptake in clinical practice and reimbursements from insurers vary substantially across the world (table 2). ^{18}F-FDG PET is reimbursed by the US Centers for Medicare and Medicaid Services if used to exclude Alzheimer's disease in patients who meet the diagnostic criteria for both Alzheimer's disease and frontotemporal lobar degeneration. Most national health systems in Europe authorise reimbursement of ^{18}F-FDG PET if differential diagnosis is required for Alzheimer's disease and frontotemporal dementia. Of

	Abnormality	Pathology
MRI		
Regional anatomy	Decreased volume of hippocampus and other temporal lobe structures	Tissue loss and neurodegeneration
PET		
^{18}F-fluorodeoxyglucose PET	Decreased uptake in posterior cingulate-precuneus and temporoparietal cortex	Glucose hypometabolism and neurodegeneration
^{11}C-PiB and fluorinated tracers for amyloid PET*	Increased cortical retention	Deposition of β-amyloid in the cortex
CSF measures		
Aβ42 or Aβ42:Aβ40	Decreased concentration or ratio	Abnormal metabolism of β-amyloid
Total tau and hyperphosphorylated tau	Increased concentration	Neuronal damage and accumulation of tau pathology; hyperphosphorylated tau is more specific for Alzheimer's disease neurodegeneration

Tau-PET is still under development and, therefore, is not included. PiB=Pittsburgh compound. Aβ=fibrillar β-amyloid. *Using tracers such as florbetapir, flutemetamol, and florbetaben.

Table 1: **Biomarkers for the diagnosis of Alzheimer's disease**

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For **The Alzheimer's Association** see https://www.alz.org

For **The Radiological Society of North America** see https://www.rsna.org/qiba

For more on **AMYPAD** see http://www.amypad.org

Panel 2: Prodromal Alzheimer's disease

Criteria for mild cognitive impairment[17–19]

- New-onset cognitive dysfunction reported by the patient, relatives, or physician that have lasted for at least the previous 6 months, particularly for episodic memory, and occasionally difficulty with language, visuospatial tasks, or topographic orientation
- Independence maintained in completing daily activities, although some may be performed to a lower standard than previously (eg, not as efficiently or with help)
- Major behavioural disturbances are mostly absent or mild (eg, in the form of sleep disorders, apathy, or depression); if dominant, other diagnoses (eg, frontotemporal lobar degeneration or dementia with Lewy-bodies) should be considered
- Neurological examination results are normal; if parkinsonism is present, differential diagnoses should be considered (eg, dementia with Lewy-bodies, rare genetic forms of Alzheimer's disease, or frontotemporal lobar degeneration)
- Mini-Mental State Examination score of 24–30
- Consistent abnormal performance compared with mean age-specific and education-specific values on memory tests
- Symptoms are unexplained by psychiatric history and assessment
- Structural imaging and laboratory examinations exclude non-degenerative and metabolic causes

Biomarker assessments

- Medial temporal (mainly hippocampal) atrophy on MRI supports a neurodegenerative process that can suggest Alzheimer's disease, but also other disorders (eg, dementia with Lewy bodies or frontotemporal lobar degeneration); atypical (neocortical) presentations might spare the medial temporal regions, especially in patients younger than 65 years
- Reduced cortical metabolism on ^{18}F-fluorodeoxyglucose PET in posterior cingulate-precuneus and temporoparietal cortex increases the likelihood that Alzheimer's disease is the cause of cognitive impairment, whereas normal PET findings suggest no neurodegenerative disease
- Abnormal CSF protein concentrations indicating abnormal amyloid metabolism (low fibrillar β-amyloid [Aβ]42 concentration or a low ratio of Aβ42 to Aβ40) and neuronal damage (high total tau and hyperphosphorylated tau concentrations) increase the likelihood that Alzheimer's disease is the cause of the cognitive impairment, whereas the combination of a normal Aβ42 concentration and normal Aβ42:Aβ40 in CSF make Alzheimer's disease very unlikely
- Absence of brain amyloidosis on amyloid PET (using tracers such as florbetapir, flutemetamol, and florbetaben) makes Alzheimer's disease a very unlikely cause of cognitive impairment, whereas positive amyloid PET supports Alzheimer's disease as the cause in young patients because the a priori risk of being amyloid positive is lower than in older people, among whom a substantial proportion of cognitively intact individuals are amyloid positive
- A positive result for one amyloidosis biomarker and one neurodegeneration biomarker is strongly associated with clinical progression over time and the development of disability and dementia within 5–7 years

Diagnosis

- Patients meeting the criteria for mild cognitive impairment and with positive biomarkers for Alzheimer's disease should be diagnosed as having mild cognitive impairment due to Alzheimer's disease or prodromal Alzheimer's disease[2,9]

note, the reimbursements are for image acquisition and traditional subjective visual readout,[39] which is operator dependent.[40]

MRI scanning is usually reimbursed in Europe and North America, but mostly for exclusion of alternative causes of cognitive impairment (non-degenerative or surgical causes) rather than the positive diagnosis of Alzheimer's disease through assessment of, for example, medial temporal atrophy. In 2009, measurement of CSF biomarkers was reimbursed in only about half of European countries.[41] In Italy, CSF biomarkers are reimbursed by the national health system only in Umbria, out of the 20 Italian regions.[38] Although amyloid PET with fluourinated tracers is available in clinics in some European countries, its use is highly restricted (table 2).

Non-evidence-based factors affect the use of diagnostic biomarkers in clinics

The inconsistent evidence on the usefulness of biomarkers for Alzheimer's disease has led to their exclusion from most evidence-based guidelines. Importantly, the development of clinical guidelines is a lengthy procedure and does not provide ready means for criteria to be easily updated as evidence accumulates. The practice parameters from the American Academy of Neurology for the diagnosis of dementia, which are now over a decade old, state that there is not enough evidence to support or refute the use of PET, CSF, or other biomarkers for the diagnosis of Alzheimer's disease.[42] The European guidelines, which were last updated in 2012,[43] state that, in clinical practice, CT and MRI should be used to exclude (usually non-degenerative) causes of dementia (class I evidence) and that biomarkers should be used to confirm diagnosis only in selected cases. The evidence for ^{18}F-FDG PET and CSF biomarkers is rated as class II and class III, respectively, for discriminating between Alzheimer's disease, frontotemporal lobar degeneration, and dementia with Lewy bodies.[43] The only biomarker recommended by the Alzheimer's Association and the Amyloid Imaging Task Force to aid a specific diagnosis of Alzheimer's

	MRI	^{18}F-fluorodeoxyglucose PET	Amyloid PET	CSF measures
France	No restrictions on prescribing; social security and private insurance reimbursement	Indicated for early diagnosis of AD, atypical presentation, or suspected FTLD, and useful for diagnosis of probable AD; social security and private insurance reimbursement	Indicated to estimate β-amyloid neuritic plaque density, with clinical evaluation, to diagnose AD in patients with cognitive decline; no reimbursement	No indication restrictions on prescribing; social security and private insurance reimbursement
Germany	No restrictions on prescribing; health insurance reimbursement	No restrictions on prescribing; no formal reimbursement, but individual exceptions might be made by health insurance (criteria unclear)	Indicated to estimate β-amyloid neuritic plaque density, with clinical evaluation, to diagnose AD in patients with cognitive decline; no reimbursement	Indicated by DGN for ordinary memory assessment in tertiary clinics and sometimes other specialised practices; health insurance reimbursement, but outpatient costs, which include lumbar puncture
Italy	Indicated in routine use, but not recommended for differential diagnosis of disorders causing dementia except between AD and VD, and between AD and FTLD; in practice, acquisition without contrast can be reimbursed once by the National Health Service (approx €250–300)	Indicated by National Health Service for differential diagnosis between AD and VD, and between AD and FTLD; National Health Service reimbursement	Indicated to estimate β-amyloid neuritic plaque density, with clinical evaluation, to diagnose AD in patients with cognitive decline; reimbursement as for brain ^{18}F-fluorodeoxy-glucose PET, but additional costs for fluorinated tracers should be covered by the hospital budget	No restrictions on prescribing; no reimbursement except by the National Health Service in Umbria[38]
Netherlands	Indicated for assessment of dementia; health insurance reimbursement	Indication for FTLD and unexplained dementia; health insurance reimbursement	Indicated to estimate β-amyloid neuritic plaque density, with clinical assessment, to diagnose AD in selected patients with cognitive decline; reimbursement under discussion	Indicated for assessment of dementia, especially in young patients; health insurance reimbursement
Spain	No formal indication; social security reimbursement	No restrictions on prescribing, but widely recommended for differential diagnosis between AD and other dementias; social security reimbursement	Indicated by AMPS to estimate β-amyloid neuritic plaque density, with clinical evaluation, to diagnose AD in patients with cognitive decline; social security reimbursement	No restrictions on prescribing and frequently used in the same patients as amyloid PET; no reimbursement
Sweden	Indicated for ordinary memory assessment in tertiary clinics; reimbursed by clinics	Indicated in tertiary clinics to confirm unclear diagnosis after ordinary memory assessment; reimbursement by clinics	Indicated in highly selected patients with unclear diagnosis after ordinary memory assessment at tertiary clinics; reimbursement by clinics	Indicated for ordinary memory assessment in tertiary clinics; reimbursement by clinics
Switzerland	No restrictions on prescribing; health insurance reimbursement	Indicated by the Health-Care Benefits Regulation as second-level investigation in unclear cases, if assessed by a neurologist, psychiatrist, or geriatrician, age <80 years, MMSE score ≥10, disease duration <5 years, and no previous brain PET or SPECT; health insurance reimbursement	Indicated to estimate β-amyloid neuritic plaque density, with clinical assessment, to diagnose AD in patients with cognitive decline; no reimbursement	No restrictions on prescribing, but under discussion; partly reimbursed by health insurance
United Kingdom	Indicated by NICE for all patients being investigated for dementia; reimbursement by National Health Service	Indicated by NICE for differentiation between AD, VD, and FTLD; reimbursement by National Health Service	Indicated by RCR-RCP in highly selected patients with cognitive impairment and suspected AD that is unclear after comprehensive assessment by a dementia expert and conventional imaging work-up, when knowledge of the presence or absence of amyloid is expected to increase diagnostic certainty and direct management, if persistent or progressive unexplained memory impairment is confirmed by standard tests, and/or if clinical presentation is unusual, at an early age (<65 years), or both; no reimbursement, but might be available in some centres by local arrangements	Indicated by NICE if Creutzfeldt–Jakob disease or other forms of rapidly progressive dementia are suspected, done in some tertiary clinics, especially for young patients (<65 years); reimbursement by National Health Service

AD=Alzheimer's disease. FTLD=frontotemporal lobar degeneration. DGN=Die Deutsche Gesellschaft für Neurologie. VD=vascular dementia. AMPS=Agencia Española de Medicamentos y Productos Sanitorios. MMSE=Mini Mental State Examination. NICE=National Institute for Health and Care Excellence. RCR-RCP=Royal College of Radiologists and Royal College of Physicians.

***Table 2*: Indications for prescription and reimbursement of neuroimaging biomarkers in neurodegenerative disorders associated with dementia in different European countries**

disease is amyloid PET, which is very expensive.[44] Several local (national, regional, or single centre) guidelines support the use of biomarkers, but inclusion has usually been driven by active scientific groups or societies, which underscores the lack of a common framework to ensure consistency.[45,46]

Without consistency, clinicians might base the use of biomarkers on practical considerations that reflect resources and experience, rather than on clinical and evidence-based considerations. In an Italian study, the choice of neuroimaging technique (CT, MRI, or ^{18}F-FDG PET) in the workup of dementia was driven as much by test availability, physicians' familiarity with the technology, and waiting time for patients as by the clinically relevant parameters, such as the patient's age, severity of cognitive impairment, or the diagnostic question (eg, clinical suspicion of cerebrovascular disease).[47] If multiple means of determining the same pathology are available, financial considerations can take precedence over other factors. In the case of brain amyloid detection, there are pros and cons of using amyloid PET or CSF biomarkers in terms of availability, reproducibility,

cost, and clinicians' and patients' acceptance of and attitude towards the methods.[48,49] In France, CSF examination is preferred over amyloid PET because the latter is not reimbursed despite being authorised.[50] Irrespective of these limitations, the increasing availability of biomarkers and pressure by increasingly informed patients makes the development of recommendations for the use of biomarkers for diagnosis in people with mild cognitive impairment urgent.

Use of diagnostic biomarkers in the absence of a treatment that delays disease progression

The net result of all the challenges discussed in relation to the development of biomarkers for Alzheimer's disease is their delayed and uncoordinated penetration into routine clinical use. Pharmacological treatment able to delay progression of Alzheimer's disease might have substantial benefits, but also side-effects.[51,52] Accurate diagnosis of Alzheimer's disease in the prodromal stage will, therefore, be paramount to minimise the risk-to-benefit ratio. Several clinical trials of promising drugs are due to be reported (eg, aducanumab, gantenerumab, crenezumab, azeliragon, inteperdine, AADvac-1, and C2N 8E12), but we cannot wait until licensing to begin adapting clinical practice.[53] Moreover, even in the absence of such drugs, the advantages of an accurate diagnosis justify the use of advanced diagnostic technology.[54] Knowing the cause of an individual's cognitive impairment before the onset of dementia enables delivery of timely and appropriate personalised care, including counselling and planning, prevents the use of inappropriate medications and ancillary investigations, and allows the eventual implementation of appropriate steps to prevent unsafe behaviours (eg, driving) and manage symptoms.[54] Furthermore, such knowledge might lead to recruitment to research studies and clinical trials. In Europe and the USA, less than 50% of people with dementia receive a formal diagnosis in primary care.[55] Access to specialised care, however, is limited for most patients. Increased use of validated biomarkers into routine care might leverage the provision of broader access to diagnostic and treatment options via specialist care resources for all people who present with symptoms of a neurodegenerative disorder.

A five-phase framework for development of Alzheimer's disease biomarkers

The development and use of biomarkers for screening and delivery of individualised treatment in oncological patients are much more advanced than those in people with Alzheimer's disease. In 2001, Pepe and colleagues[56] devised a five-phase framework for the development of biomarkers to screen for cancer in the general population. Each phase had one or two primary aims with pertinent outcome measures, as well as several secondary aims. From this oncology framework, we have made adaptations to create a similar framework for Alzheimer's disease (table 3).

Several basic differences in biomarker validation have to be taken into consideration due to the more advanced knowledge available in oncology, and to reflect the current understanding of Alzheimer's disease.[57] First, Alzheimer's disease biomarkers are intended for diagnosis rather than screening in the general population. Second, the access to brain samples at autopsy to obtain neuropathological data can be difficult, although neuropathology is the current gold standard for Alzheimer's disease diagnosis. Third, interventions that alter the course of Alzheimer's disease positively and, therefore, can have substantial effects on phase 5 outcomes (mortality, morbidity, and disability associated with Alzheimer's disease), do not yet exist.

Research priorities in Alzheimer's disease for launching phase 4 studies

We have reviewed evidence on the validity of Alzheimer's disease biomarkers, restricting the clinical context to the diagnosis of prodromal Alzheimer's disease. Prognosis in patients with mild cognitive impairment is uncertain—up to 50% do not develop dementia—which increases the importance of making an accurate diagnosis to identify and manage properly those with progressing neurodegeneration. The initiative included the Alzheimer's disease biomarkers with the best evidence of validity, which we term core biomarkers. Tau PET was not included because it is an emerging technology still in the earliest stages of development.[58] However, the roadmap we propose provides a general framework that will be applicable to other technologies or techniques, including tau PET.

The methods and results of this evidence review have been reported in detail.[54,57,59–64] Briefly, we did a literature review with harmonised strings for the individual aims in each phase (panel 3). The core biomarkers have been validated to varying degrees, with none having phase 5 data available and only preliminary phase 4 evidence being available for a few aims for ^{18}F-FDG PET and CSF biomarkers (table 4). Unsurprisingly, given that individual biomarkers have been assessed so variably, evidence from studies comparing combinations of biomarkers is very limited (phase 3 secondary aims two and three). Here we summarise the conclusions of our literature review for each potential biomarker and highlight research priorities. We present neuropsychology first because it has the role of being a gateway to subsequent assessments (only patients testing positive to neuropsychological tests will undergo biomarker assessment). The following biomarkers are listed from those developed earliest.

Neuropsychology

Neuropsychological tests are not suitable as biomarkers for Alzheimer's disease,[59] but can serve as gatekeeper tests for the use of biomarkers (table 5). In particular, neuropsychological tests show objective impairment, which allows distinction between mild cognitive

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	Primary and secondary aims	Adaptations from oncology to AD
Phase 1: preclinical exploratory studies	Primary aims: (1) identify leads for potentially useful biomarkers; (2) prioritise identified leads	No substantial change
Phase 2: clinical assay development for Alzheimer's disease pathology	Primary aims: (1) estimate the frequency of true-positive and false-positive results or ROC, and assess ability to distinguish individuals with and without Alzheimer's dementia Secondary aims: (1) optimise procedures for assays and their reproducibility within and between laboratories; (2) determine the relation between phase 1 biomarker measurements made in tissues and those made in phase 2 studies in non-invasively collected clinical specimens; (3) assess variables (eg, sex and age) associated with biomarker status or concentration in controls (eg, healthy individuals);* (4) assess variables, especially disease characteristics, associated with biomarker status or level	Established disease in cancer is believed to correspond to overt dementia in AD; the preferable standard of reference in AD is pathology, although AD dementia is acceptable if there is reason to believe that most individuals being assessed have AD pathology (eg, NINCDS-ADRDA probable AD dementia)[3]
Phase 3: retrospective studies using longitudinal data available in repositories	Primary aims: (1) assess the capacity of the biomarker to detect early disease†; (2) define criteria for a positive screening test in preparation for phase 4 Secondary aims: (1) explore the effects of covariates on the discriminatory abilities of the biomarker before clinical diagnosis; (2) compare biomarkers to select the most promising; (3) develop algorithms for likelihood of positive results based on combinations of biomarkers; (4) determine required interval between biomarker testing if repeated testing is of interest in phase 4	In contrast to phase 3 studies in oncology, which are retrospective, nested, case-control studies, AD requires prospective longitudinal repository studies, in which the biomarker is measured at baseline in individuals with MCI and AD status ascertained at follow-up, preferably by AD pathology, but also by incident AD dementia or cognitive progression; as in cancer, AD biomarker results would not be used for diagnosis or treatment
Phase 4: prospective diagnostic accuracy studies	Primary aims: (1) determine the accuracy of core biomarkers in the clinical setting by calculating frequencies of positive and false-positive detection Secondary aims: (1) describe the characteristics of disease detected by the biomarker test, particularly with regard to potential benefits incurred by early detection; (2) assess the feasibility of implementing case-finding programmes and likely adherence of individuals with positive test results to work-up schedules and treatment recommendations; (3) make preliminary assessments of the effects of biomarker testing on disease-associated costs and mortality; (4) monitor disease diagnosed clinically but not detected by biomarker testing	The major difference with phase 4 in oncology is that studies will not involve clinically asymptomatic individuals; AD studies would include symptomatic but non-demented (MCI) patients and, therefore, would need to be done in highly specialised clinics that have guidelines for the collection, measurement, and interpretation of biomarkers; as in oncology, AD biomarker results would be used for diagnosis and treatment
Phase 5: disease burden reduction studies	Primary aims: (1) estimate reductions in mortality, morbidity, and disability associated with biomarker testing Secondary aims: (1) obtain information about costs of biomarker testing and treatment and per life saved or quality-adjusted life year gained; (2) assess adherence to testing and work-up in various settings; (3) compare different biomarker testing protocols, approaches to treating test-positive individuals in regards to effects on mortality, costs, or both	No adaptation needed, although the achievement of phase 5 outcomes is unlikely until treatments able to delay progression are available

AD=Alzheimer's disease. ROC=receiver operating curve. NINCDS-ADRDA=National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association. MCI=mild cognitive impairment. *Thresholds might need to be defined separately for different target subpopulations. †MCI or prodromal AD.

***Table 3*: Five-phase framework to develop biomarkers for early diagnosis of Alzheimer's disease**

impairment and subjective cognitive complaints. The positive and negative predictive values of neuropsychology biomarkers are dependent on the psychometric properties of these tests' sensitivity and specificity and the prevalence of the target disease in the patients undergoing assessment.

In the evidence review on neuropsychology, Cerami and colleagues[2] focused on delayed free and cued recall tasks because these represent the most sensitive measures of memory decline in the typical presentation of Alzheimer's disease and have a reasonable degree of specificity for the typical dysfunction of Alzheimer's disease. They found that multiple tests are available to assess the same brain function, but they are not standardised for administration, scoring, and normative values. Research priorities, therefore, are to compare the diagnostic accuracy of these tests and harmonise them by consensus into a standard test with multilingual versions and pertinent normative values. The standardised test should include parts that would be sensitive for atypical presentations of Alzheimer's disease.

Medial temporal atrophy

Ten Kate and colleagues[61] reviewed the evidence for two different ways of assessing medial temporal atrophy: visual rating, which is easily done in clinical settings, and volumetric assessment, which is a time-consuming manual procedure, although automated algorithms can also be used and save a substantial amount time. Both

these methods require extensive experience that is more often available in research than in clinical settings. Medial temporal atrophy is the only biomarker for which phase 1 and phase 2 studies are almost completed, and, therefore, is furthest through the validation process; the five validation phases should be sequentially ordered (ie, early phases should be completed before later downstream phases for the whole validation process to be valid). The amount of work completed, however, is probably due more to atrophy being one of the oldest and most accessible and studied Alzheimer's disease biomarkers than to coordination of activities and projects within the scientific community. As for most Alzheimer's disease biomarkers, only sparse preliminary data on the practical feasibility (phases 4 and 5) of the visual assessment of medial temporal atrophy are available. Moreover, similar to other Alzheimer's disease biomarkers, this assessment has limited specificity when used alone, and its usefulness in combination with other biomarkers must be assessed in phases 4 and 5.

The strength of medial temporal atrophy as a biomarker lies in the feasibility of visual assessment with a well consolidated technique,[65] and the reliability of HarP[36] against which new automated algorithms can be validated. Visual assessment has the potential to be rapidly implemented in clinical practice, although in the long term, automated volumetric analysis, which could improve reliability, might become the standard tool.

Panel 3: Search strategy and selection criteria

For each core biomarker for Alzheimer's disease, independent searches were done for each primary and secondary aim in the five roadmap phases. Harmonised literature search strings are presented. Studies were included if they assessed dementia (phase 2) or mild cognitive impairment (phases 3–5), and included appropriate gold or reference standards, control groups, and outcome measures consistent with the specific phase targets.

Phase 1: preclinical exploratory studies

No strings

Phase 2: clinical assay development for Alzeheimer's disease pathology

Primary objective

1 ("accuracy" OR "sensitivity" OR "specificity" OR "ROC" OR "predictive value") AND ("Alzheimer*") AND ("Healthy controls" OR "Cognitively normal" OR "controls" OR "normal") AND (<biomarker-specific string>) AND (other disease/eg, DLB—if pertinent)

Secondary objectives

1 ("standardization" OR "visual" OR "measure" OR "assessment" OR "reading" OR "quantification" AND ("reproducibility OR "reliability" OR "agreement") AND ("Alzheimer*") AND (<biomarker-specific string>)
2 ("autopsy" OR "autoptic" OR "pathology" OR "neuropatholog*" OR "istopathol*") AND ("Alzheimer*") AND (<biomarker-specific string>) AND (other disease/eg, DLB—if pertinent)
3 ("effect" OR "association" OR "covariates") AND ("factor" OR "habit*" OR "age" OR "sex" OR "gender" OR "education" OR "life-style" OR "risk factor*") AND ("Healthy controls" OR "Cognitively normal" OR "controls" OR "normal") AND (<biomarker-specific string>)
4 ("effect" OR "association" OR "covariates") AND ("factor" OR "habit*" OR "age" OR "sex" OR "gender" OR "education" OR "life-style" OR "risk factor*") AND ("Alzheimer*") OR ("MCI" OR "mild cognitive impairment" OR"prodromal") OR (other disease/eg, DLB—if pertinent) AND (<biomarker-specific string>)

Phase 3: retrospective studies using longitudinal data available in repositories

Primary objectives

- ("follow-up" OR "followup" OR "conversion" OR "progression" OR "decline" OR "predict*") AND ("MCI" OR "mild cognitive impairment" OR"prodromal") AND (<biomarker-specific string>)
- [("cut-off" OR "cut-point" OR "measure" OR "assessment") added for the threshold for positivity]

Secondary objectives

1 ("effect" OR "association" OR "covariates") AND ("factor" OR "habit*" OR "age" OR "sex" OR "gender" OR "education" OR "life-style" OR "risk factor*") AND ("Alzheimer*") OR ("Healthy controls" OR "Cognitively normal" OR "controls" OR "normal") OR ("MCI" OR "mild cognitive impairment" OR"prodromal") AND (<biomarker-specific string>)
2 ("follow-up" OR "followup" OR "conversion" OR "progression" OR "decline" OR "predict*" OR "cut-off" OR "cut-point" OR "measure" OR "assessment") AND ("combinat*" OR "associat*" OR "compar*") AND ("Alzheimer*") AND ("MCI" OR "mild cognitive impairment" OR"prodromal") AND (other disease/eg, DLB—if pertinent)
3 ("follow-up" OR "followup" OR "conversion" OR "progression" OR "decline" OR "predict*" OR "cut-off" OR "cut-point" OR "measure" OR "assessment") AND ("combinat*" OR "associat*" OR "compar*") AND ("Alzheimer*") AND ("MCI" OR "mild cognitive impairment" OR"prodromal") AND (other disease/eg, DLB—if pertinent)
4 ("follow-up" OR "followup" OR "conversion" OR "progression" OR "decline" OR "predict*" OR "cut-off" OR "cut-point" OR "measure" OR "assessment") AND ("periodic*" "repeated" OR "time") AND ("Alzheimer*") AND ("MCI" OR "mild cognitive impairment" OR"prodromal")

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Phase 4: prospective diagnostic accuracy studies

Primary objective

1 ("diagnosis" OR "treatment") AND ("Alzheimer*") AND ("MCI" OR "mild cognitive impairment" OR"prodromal") AND (<biomarker-specific string>)

Secondary objectives

1 ("clinical diagnosis" OR "treatment" OR "memory clinic") AND ("benefits" OR "outcome" OR "improve*") AND ("Alzheimer*") AND ("MCI" OR "mild cognitive impairment" OR"prodromal") AND (<biomarker-specific string>)
2 ("clinical diagnosis" OR "treatment" OR "memory clinic") AND ("benefit*" OR "compliance" OR "mortality" OR "morbidity" OR "QoL" OR "quality of life") AND ("Alzheimer*") AND (<biomarker-specific string>)
3 ("clinical diagnosis" OR "treatment" OR "memory clinic") AND ("benefit*" OR "compliance" OR "mortality" OR "morbidity" OR "QoL" OR "quality of life" OR "cost*") AND ("Alzheimer*") AND (<biomarker-specific string>)
4 ("clinical diagnosis" OR "memory clinic" OR "criteria" OR "recommendation*") AND ("accuracy" OR "sensitivity" OR "specificity" OR "ROC" OR "predictive value" OR "concordance" OR "confirm" OR "negative detection rate" OR "negative referral rate" OR "false negative rate") AND ("Alzheimer*") AND (<biomarker-specific string>)

Phase 5: disease burden reduction studies

Primary objective

1 ("diagnosis" OR "detection") AND ("benefit*" OR "compliance" OR "mortality" OR "morbidity" OR "QoL" OR "quality of life" OR "financial impact" OR "cost*" OR "effectiveness") AND ("Alzheimer*") AND (<biomarker-specific string>)

Secondary objectives

1 ("diagnosis" OR "detection") AND ("benefit*" OR "compliance" OR "mortality" OR "morbidity" OR "QoL" OR "quality of life" OR "outcome*") AND ("financial impact" OR "cost*" OR "effectiveness") AND ("Alzheimer*") AND ("MCI" OR "mild cognitive impairment" OR"prodromal")
2 ("diagnosis" OR "treatment") AND ("benefit*" OR "compliance" OR "mortality" OR "morbidity" OR "QoL" OR "quality of life") AND ("primary care" OR "second level" OR "third level") AND "memory clinic" AND "cost*" AND ("Alzheimer*") AND (<biomarker-specific string>)
3 ("diagnosis" OR "treatment") AND ("protocol" OR "recommendation*" OR "criteria") AND ("benefit*" OR "compliance" OR "mortality" OR "morbidity" OR "QoL" OR "quality of life") AND ("financial impact" OR "cost*" OR "effectiveness") AND ("Alzheimer*") AND (<biomarker-specific string>)

Biomarker-specific strings

Amyloid PET

- ("Positron Emission Tomography" OR "PET") AND ("PIB" OR "Pittsburgh compound b" OR "Pittsburgh compound-b" OR "Florbetapir" OR "AV45" OR "AV-45" OR "Amyvid" OR "Flutemetamol" OR "Vizamyl" OR "GE067" OR "Florbetaben" OR "av-1" OR "BAY94-9172" OR "Neuraceq")

CSF measures

- ("cerebrospinal fluid" OR "CSF") AND ("amyloid-β*" OR "Aβ*" OR "Abeta*" OR "beta-amyloid*" OR "Tau" OR "Phospho-Tau" OR "P-tau")

^{18}F-fluorodeoxyglucose PET

- ("fluorodeoxyglucose" OR "FDG" OR "18F-FDG") AND ("positron emission tomography" OR "PET")

Hippocampal or medial temporal atrophy

- ("MTA" OR "medial temporal" OR "hippocamp*")

Neuropsychology

- "RAVLT" OR "auditory verbal learning test" OR "CVLT" OR "California verbal learning test" OR "FCSRT" OR "Free and cued selective reminding test" OR "Grober-Buschke" OR "cued memory task" OR "word list memory task" OR "immediate recall memory" OR "delayed recall memory"

DLB=dementia with Lewy bodies.

HarP is now being implemented into algorithms and should help calibrate the various volumetric approaches. Heterogeneous reference populations used to establish normative values, differences in measurements across algorithms, and short follow-up have led to no thresholds for positivity in volumetric analysis yet being validated, which has weakened the clinical usefulness of the work so far. The major weakness of this biomarker is its poor specificity to distinguish non-Alzheimer's causes of cognitive impairment. Research priorities are to define standard operating procedures for automated algorithms and to rerun phase 3 studies to assess automated hippocampal volumetric analysis (table 5).

^{18}F-FDG PET

^{18}F-FDG PET is also at a more advanced stage of validation than most other Alzheimer's disease biomarkers.[60] However, the greater availability of phase 4 preliminary data on the clinical relevance and cost-effectiveness of ^{18}F-FDG PET in patients with atypical or early-onset Alzheimer's disease is weakened by incomplete earlier phases. In particular, there is insufficient evidence on the effect of covariates, such as *APOE* genotype, disease duration, or cortical atrophy on hypometabolism in patients with Alzheimer's disease (phase 2, secondary aim 4). The studies assessing the capacity of ^{18}F-FDG PET to detect prodromal Alzheimer's disease in phase 3 (primary aim 1) might contain more

	Phase 1: preclinical exploratory studies; PA	Phase 2: clinical assay development for Alzheimer's disease pathology					Phase 3: retrospective studies using longitudinal data available in repositories						Phase 4: prospective diagnostic accuracy studies					Phase 5: disease burden reduction studies; PA
		PA	SA1	SA2	SA3	SA4	PA1	PA2	SA1	SA2	SA3	SA4	PA	SA1	SA2	SA3	SA4	
MRI medial temporal atrophy*	Full	Full	Part	Full	Full	Full	Full	PE	Part	Part	Part	NA	NE	NE	NE	NE	NE	NE
^{18}F-fluorodeoxy-glucose PET	Full	Full	Full	Full	Full	Part	Full	Part	PE	Part	Part	PE	NE	PE	NE	PE	NE	NE
^{11}C-PiB and fluorinated tracers for amyloid PET†	Full	Full	Part	Full	Part	Part	Full	Part	NE	Part	Part	PE	NE	NE	NE	NE	NE	NE
CSF measures (Aβ42 or Aβ42:Aβ40 or total tau and hyperphosphorylated tau)	Full	Full	PE	Full	Part	Part	Full	Part	Part	Part	Part	PE	PE	NE	NE	NE	NE	NE

PA=primary aim. SA=secondary aim. Full=Phase fully achieved (no need to collect further evidence). Part=Phase partly achieved (studies available but replication or completion is required). PE=only preliminary evidence available. NA=not applicable. NE=no evidence available. PiB=Pittsburgh compound. Aβ=fibrillar β-amyloid. *Assessments represent the least developed level between visual and volumetric medial temporal atrophy. †Using tracers such as florbetapir, flutemetamol, or florbetaben.

Table 4: **State of completion of biomarkers development in Alzheimer's disease for the five phases in the strategic roadmap**

variability than would be seen after completion of phase 2 studies, and that could hide greater potential for ^{18}F-FDG PET accuracy. This uncertainty, in addition to the availability of different readout procedures, each of which has its own positivity threshold (phase 3, primary aim 2), might contribute to the highly variable accuracy seen for this biomarker in detecting prodromal Alzheimer's disease (table 5).[66]

CSF measures

CSF biomarkers for Alzheimer's disease are at an advanced stage of development.[63] However, the available manual immunoassays are sufficiently stable only when used in experienced laboratories with quality control procedures (phase 2, secondary aim 1). A potentially important advancement has taken place, which is the development of fully automated assays based on electrochemiluminescence.[67] These novel assays feature coefficients of variability almost one order of magnitude lower than those of the traditional manual assays. Nevertheless, a standardised optimum protocol for preanalytical handling of CSF samples needs to be developed and implemented. We do not anticipate the need to rerun all phase 2 and 3 studies on the newer and future assays, but the cutoff values for normal ranges will need to be defined for all immunoassays with use of a suitable reference (preferably neuropathology; phase 3, primary aim 2). Several research priorities for CSF biomarkers identified in this roadmap are already underway, such as the development of international certified reference materials to better bridge results between different assays (table 4).

Amyloid PET

Despite consensus on the equivalence of the three regulatory-approved fluorinated tracers used for amyloid PET, the interpretation of findings from studies in phase 3 is complicated by imperfect standardisation of comparative reading or quantification procedures (phase 2, secondary aim 1) and thresholds for positivity (phase 3, primary aim 2).[64] The effect of covariates on cases (phase 2, secondary aim 4) and controls (phase 2, secondary aim 3) has been assessed quite extensively but will be more reliable when a harmonised procedure for all tracers is developed. Reliability of results might improve when a harmonised procedure for all tracers (eg, that being developed by the Centiloid Project[68]) is more widely implemented. Similarly, a harmonised procedure might affect the ability of this biomarker to detect prodromal Alzheimer's disease (phase 3, primary aim 1). This objective was deemed to be fully achieved based on the studies published so far, but uncertainty remains.[69] Additionally, a harmonised procedure relies on the assumption that the different tracers have similar discriminative abilities, a notion for which there is only preliminary evidence.

Phase 3 studies will also need to address the effects of clinical covariates on the detection of Alzheimer's disease pathology in patients with mild cognitive impairment (phase 3, secondary aim). Evidence indicates that individuals with borderline retention levels but who are still within normal ranges could be so-called accumulators (ie, individuals in whom brain amyloidosis is increasing and who would thus become positive within a short time). Understanding accumulators is relevant, as findings in this group might alter the threshold for positivity (phase 3, secondary aim 4, table 4).

These uncertainties notwithstanding, findings from some small-scale phase 4 studies are already available, and collaborative efforts between researchers and tracer developers have led to ongoing larger-scale phase 4 studies (IDEAS and AMYPAD).

Tau PET

The emergence of PET tracers that target deposits of abnormally hyperphosphorylated tau protein, a key pathological hallmark of Alzheimer's disease, has opened up the possibility of using PET to measure the prevalence

	Phase 2			Phase 3					
	SA1	SA3	SA4	PA1	PA2	SA1	SA2	SA3	SA4
Neuropsychology	Define standard neuropsychology tests, sensitive also to atypical AD presentations	Establish normative values	NP	NP	Define threshold to proceed with biomarker testing	NP	NP	NP	NP
Hippocampal volume	Define SOPs for automated algorithms	NP	NP	Assess prognostic accuracy	Threshold definition	Assess impact of covariates on diagnostic accuracy	NP	NP	NP
^{18}F-fluorodeoxy-glucose PET	NP	NP	Assess effects of covariates on retention	Reassess diagnostic accuracy	Harmonise and validate reading criteria; define threshold	NP	NP	NP	NP
CSF Aβ42 or Aβ42:Aβ40 or total tau and hyper-phosphorylated tau	Standardise preanalytical handling; validate fully automated immunoassays	Assess effects of non-AD pathologies on concentrations	Complete assessment of effects of covariates on concentrations	NP	Reassess thresholds with newly validated standards	NP	Redefine optimum combination of biomarkers for newly validated standards	Define optimum combination with other biomarkers	Determine within-individual changes over time with newly validated standards
Amyloid PET*	Assess comparability, reproducibility SOPs, and readout methods	Assess effects of covariates on retention	Assess effects of disease characteristics and covariates on retention	Reassess diagnostic accuracy if new standard is defined	Harmonise reading criteria and improve threshold definition	Assess impact of covariates on diagnostic accuracy	Compare with other biomarkers (mainly in CSF) with newly validated standards	Define optimum combination with other biomarkers	Determine meaning of intermediate or dubious retention and set interval between repeated testing if useful

SA=secondary aim. PA=primary aim. AD=Alzheimer's disease. NP=not a priority. SOPs=standard operating procedures. Aβ=fibrillar β-amyloid. *With tracer florbetapir, flutemetamol, or florbetaben.

***Table 5*: Research priorities to complete biomarker validation**

of different forms of tau deposits in the brains of patients with Alzheimer's disease and other tau-related pathologies. These tracers have shown high specificity for tau pathology in vitro (specifically to 3R/4R paired helical filamentous tau aggregates that are characteristic of Alzheimer's disease), although the agreement between tracer binding and tau immunohistochemistry seems to be complex.[70–74] The favourable pharmacokinetics of these tracers[75–77] completes the requirements for phase 1 studies. Several small phase 2 studies have reported good discrimination between healthy volunteers and patients with Alzheimer's disease.[70,78–81] Preliminary evidence for one tracer (AV-1451) shows agreement between ante-mortem PET quantification by measurement of tracer retention and post-mortem evidence of tau pathology in patients without Alzheimer's disease (a carrier of a *MAPT* mutation, and two patients with corticobasal degeneration), although questions remain about the specific target of the tracer (phase 2, secondary aim 2).[58,82,83] Further research on tau PET imaging is needed to understand the binding characteristics of the different tracers before the clinical validity of this novel biomarker is explored further.

Combinations of biomarkers

The most widely accepted diagnostic criteria assume that the greatest accuracy can be achieved with a combination of amyloidosis biomarkers (either amyloid PET or CSF Aβ42 or Aβ42:Aβ40) with neurodegeneration markers (medial temporal atrophy, ^{18}F-FDG PET, or CSF total tau and p-tau)[11] or of amyloidosis and tauopathy markers (amyloid PET and CSF Aβ42 or Aβ42:Aβ40 or total tau and p-tau).[4] The findings with these combinations, however, are inconsistent,[59–64] and simply suggest that use of more biomarkers might improve accuracy.

To define an efficient combination of biomarkers, the discriminant ability of each needs to be assessed based on operative procedures that have successfully completed earlier phases, and in patients in whom all the tested biomarkers are simultaneously measured. Such a design is feasible for phase 3 studies of medial temporal atrophy, ^{18}F-FDG and amyloid PET, and CSF biomarkers.

Further considerations for launching phase 4 studies

Little has been achieved in phase 4 studies for any of the core Alzheimer's disease biomarkers (table 4) and completion of phases 2 and 3 is needed to proceed to phase 4 studies. We believe, however, that at least three additional conditions should be satisfied to set up methodologically sound phase 4 studies.

Biomarker testing in memory clinics

Biomarkers that are valid after completion of phases 2 and 3 will be sufficiently robust to be tested for diagnosis

***Panel 4*: Take-home messages**

Incomplete evidence of clinical validity is available on diagnostic biomarkers for Alzheimer's disease, which is adversely affecting their clinical use and reimbursement.

Aim

To define a strategic research agenda to synchronise research efforts and complete validation effectively, to get biomarkers approval for clinical use.

Action

We interpreted evidence on Alzheimer's disease biomarkers in the context of a five-phase framework for the structured validation, adapted from the development of oncology biomarkers: phase 1, preclinical exploratory studies; phase 2, clinical assay development for Alzheimer's disease pathology; phase 3, retrospective studies of longitudinal data available in repositories; phase 4, prospective diagnostic accuracy studies; and phase 5, disease burden reduction studies.

Evidence

Phase 1 is complete for all biomarkers and research priorities have been identified for phases 2 and 3, including the definition of standard procedures for reliable assessment, investigation of confounders affecting biomarker performance and thresholds, and comparison with other biomarkers to define an effective diagnostic algorithm.

Future actions

Complete phases 2 and 3 according to proposed research priorities, set up phase 4 then phase 5 studies, and define guidelines for best use of biomarkers and of combinations thereof in clinical practice.

Recommendations

Set up validation of new biomarkers according to the five-phase framework and rerun validation studies for available biomarkers lacking evidence from phase 2; biomarkers should be validated in phase 4 studies done in qualified memory clinics and after obtaining appropriate ethics approval and patients' informed consent.

and treatment in clinical settings. Some of the biomarkers will be commercial ready-to-use products, but some will not. For instance, amyloid tracers have not yet completed phase 3 but are commercially available, whereas whether automated hippocampal volumetric analysis will ever be marketed commercially, even after phase 3 is completed, is unclear. For this reason, phase 4 studies might be most appropriately done in memory clinics where data can be collected with standardised methods. This is the approach taken by a national multicentre research project in Italy involving six memory clinics that are qualified to collect CSF measures, do structural MRI following the Alzheimer's Disease Neuroimaging Initiative protocol, and assess hippocampal volume, temporoparietal hypometabolism, and amyloid load based on PET imaging. The results of this study will be used to guide the diagnosis and treatment of people with mild cognitive impairment in Italy.

Clinical guidelines

Biomarkers cannot be included in a phase 4 study without clinical guidelines for their appropriate use and on how to integrate the results as part of a patient's diagnostic workup. Clinical and neuroimaging guidelines specific to amyloid PET have been developed by Canadian, European, Italian, UK, and USA task forces.[84–88] However, these guidelines have addressed this method as a standalone biomarker, whereas in practice it will be used and interpreted in association with other biomarkers, including other measures of amyloid deposition (eg, CSF biomarkers).[89] The US clinical guidelines are being used in the IDEAS amyloid PET study (phase 4), that will obtain scans from 18 000 people.

Guidelines focusing on neuroimaging[90] take a traditional approach to imaging biomarkers, suggesting the use of traditional qualitative reading rather than semiautomated approaches as our roadmap would recommend. Biomarker-specific guidelines will need to be developed for phase 4 studies, and will need to inform use and interpretation of biomarkers in the clinical setting.

Ethical considerations

Phase 4 studies imply that biomarkers not yet approved by regulatory agencies for clinical use will eventually guide diagnosis and treatment of patients. Good Clinical Practice research frameworks will need to be followed in these studies, including ascertainment of relevant ethics approval and informed consent for storage and sharing of anonymised data. Particularly relevant to the implementation of phase 4 studies is that patients are informed about the degree of uncertainty and the readout limitations of the biomarkers being tested and how those biomarkers will be used to guide diagnosis and treatment. Guidelines for the disclosure of the diagnosis in the prodromal stage of Alzheimer's disease that include patients' preferences and needs relative to discloure procedures will need to be developed. Structured training for clinicians on how to communicate diagnoses to individuals should also be promoted.

Irrespective of guidelines, MRI-based volumetric analysis and amyloid PET are being used for profit by screening for Alzheimer's disease in individuals for whom these assessments would not be indicated. This use outside academia underscores the urgent need for the assessment and adoption of stricter rules for biomarker use in people with cognitive concerns.

Conclusions and future directions

We have identified gaps in the evidence that prevent Alzheimer's disease biomarkers from being used rationally

and cost-effectively in clinical practice, and have formulated research priorities within a five-phase roadmap to fill these gaps. We aim to influence funding agencies of health-care research, pharmaceutical companies, scientists and scientific societies, and policy makers.

The agreement on the need for further efforts of biomarker validation is not universal in the Alzheimer's disease scientific community. For instance, some researchers have acknowledged the need for more systematic validation of CSF biomarkers,[91,92] whereas others see the available evidence as being sufficient to support the use of these markers in the clinic.[93] If experts do not agree, it is unsurprising that health-care payers are reluctant to provide reimbursements. The adoption of the five-phase framework that we propose might contribute to the harmonising of biomarker validation (panel 4) and, ultimately, reduce heterogeneity of prescription and reimbursement. Our effort is not the first of this kind. An earlier attempt to develop a validation framework was proposed for quantitative imaging biomarkers for Alzheimer's disease,[94] but, maybe due to the lack of consensus, no substantial changes took place in response to that proposal.

Our five-phase roadmap requires that a given phase is addressed only after the previous ones have been completed. In practice, especially for biomarkers that have been through previous validation studies, the process will be less orderly because of factors including commercial pressure, funding opportunities, cooperation between researchers, responses by regulatory agencies, and the views from patients and society. Additionally, without a treatment that delays disease progression, phase 5 studies aimed at estimating reductions in mortality, morbidity, and disability associated with Alzheimer's disease by measurement of biomarkers are necessarily limited. Several pharmacological phase 3 trials are being done in which drugs are offered only to patients positive for specific diagnostic biomarkers.[95] Most of the drugs being investigated are amyloid-lowering agents, and the target population is patients with brain amyloidosis confirmed by amyloid PET or measurement of Aβ42 in CSF. In these trials, the biomarkers are "theranostics" (ie, tests used to select focused therapy) Should a phase 3 trial of one of these drugs show effecacy on clinical outcomes, the theranostic will also share the merit. Thus, the phase 3 study of the drug will equal to a successful phase 5 study of the theranostic biomarker.

We believe that the success of a pharmacological treatment able to delay Alzheimer's disease progression (eg, aducanumab[52]) at the prodromal stage of the disease would not make our effort obsolete. Only about 20% of patients with Alzheimer's disease are estimated to be treated with the approved, usually reimbursed, orally administered, and relatively low-cost cholinesterase inhibitors.[96] We predict that the proportion of patients treated with new drugs, some of which will be substantially more expensive and need to be given via less practical administration routes (eg, intravenously), will be even lower. New drugs will increase the relevance and urgency for accurate diagnostic tools to select the appropriate patients (ie, with presence of amyloid or tau aggregates), properly stage the disease (eg, if treatment is effective or authorised only at specific stages), and monitor response to treatment. Finally, even once effective drugs are available, many patients will not qualify for these treatments but will still need accurate diagnoses to receive the best possible alternatives. Finally, the new diagnostic or theranostic biomarkers that the very active research in the field is likely to yield[97] will also need to undergo the same five-phase process of validation that we have described. The availability of the data for the core biomarkers will facilitate such a process.

Contributors

GBF conceived the the approach to creating the framework. FB, KB, SC, KC, J-FD, VG, PG, AG, OH, KH, CRJ, FN, AN, HMS, MTK, AV, EA, SB, PB, MC, CC, BD, VG, EG, GG, SH, AL, K-OL, NM, J-LM, AM, UM, APa, APi, CP, OR, LS-A, CS, PS, JS, IS, ST, PV, P-JV, and YY acquired the data through literature reviews and research experience. All authors analysed and interpreted the data. GBF, MB, and BW, wrote the paper, which was critically reviewed by all authors for intellectual content and approved before submission.

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Diagnostic biomarkers for Alzheimer's disease: a regulatory view

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Health-care systems worldwide face an unprecedented challenge in dealing with the unmet needs of dementia diagnosis. Dementia is a clinical concept, and the diagnosis of Alzheimer's disease remains essentially based on clinical symptoms, despite the neuropathological end state of the condition being known. Several potential diagnostic biomarkers for Alzheimer's disease have been assessed in cohort studies.[1] However, for any disorder, the usefulness of biomarkers is only as good as the understanding of the disease process.

In a Policy View in *The Lancet Neurology*, Giovanni Frisoni and colleagues[2] reflect on the paradigm shift that is occurring in the diagnosis of Alzheimer's disease: from an exclusionary clinical approach towards the development of diagnostic criteria based on pathological changes associated with amyloid plaques and neurofibrillary tangles. They note that substantial technological advances in MRI and PET neuroimaging, and in CSF analysis have allowed the development of biomarkers related to neurodegeneration, cerebral β-amyloid deposition, and tau-related pathology. This view, however, implies that the amyloid hypothesis of Alzheimer's disease is correct, although it remains contested, not least in the context of the perceived failure of trials of drugs targeting brain amyloid.[3] A stimulus to move beyond over-reliance on the amyloid hypothesis should be provided by the high number of potential trial participants with mild cognitive impairment or confirmed Alzheimer's disease excluded at screening because they do not meet the amyloid biomarker inclusion criteria. Nevertheless, the

identification of biomarkers is fundamental to making therapeutic advances in this area. It has almost become a cliché that once Alzheimer's disease becomes clinically manifest, it is already too late to intervene, making early diagnosis a public health, clinical, and scientific priority.

The CNS drug pipeline looks worryingly dry. There are several reasons for this scarcity, including the obvious complexity of the CNS, a lack of interdisciplinary collaborations, and increased drug development costs and risk of clinical failure compared with other areas of drug development. In response to this dearth of new drugs and the ever-increasing burden on health-care systems, initiatives from health professionals, academic journals, and public–private partnerships, such as the Innovative Medicines Initiative and the Human Brain Project, are advancing knowledge and maintaining public interest in the topic. The European Union, however, is frequently trailing behind the USA. Companies often submit new licenses for marketing authorisation to the US Food and Drug Administration (FDA) before going to the European Medicines Agency (EMA). The year 2016, for example, was a particularly bad one for CNS drugs, including those for Alzheimer's disease, although the downward trend has been seen for several years. Since 2011, companies have submitted only 26 new neurology and psychiatry drug marketing-authorisation applications in the USA and the European Union. On average, there have been fewer than five drugs submitted per year to the FDA[4] and four to the EMA.[5]

There has been some good news in the past 5 years. Several qualifications for new methodologies in neurology and psychiatry, including biomarkers for diagnostic, prognostic, and clinical outcomes suitable for use as endpoints, have been granted by the EMA, particularly for neuroimaging and clinical endpoints that were validated with digital technology.[6] PET as an amyloid biomarker has brightened an otherwise gloomy outlook, with three new diagnostic tracers (florbetapir, flutemetamol, and florbetaben) now available. Thanks to the improved understanding of disease mechanisms, pharmacodynamic, clinical, and behavioural measures,[6] the incorporation of biomarkers in preclinical and clinical drug development has accelerated the regulatory assessment of CNS products and the creation of new guidelines for developing drugs for Alzheimer's disease at the EMA,[7] FDA,[8] and the Pharmaceuticals and Medical Devices Agency in Japan.[9]

Frisoni and colleagues' Policy View is a well equipped base camp from which to tackle the early diagnosis of Alzheimer's disease, and clearly identifies strategic priorities for biomarker research. There is much at stake. Alzheimer's disease is of enormous importance in the ageing population worldwide, and the development of accurate methods to assess the personal risk of developing this disorder reflects the mounting demand for individualised health care. A risk assessment, however, is not a prediction, although there is the danger it might be taken as such. Embracing new biomarkers without critical review has obvious ethical pitfalls. The clinical relevance of biomarkers for Alzheimer's disease must be considered in the wider context of ethics, genetic counselling, and public education.

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Genomic profiling and diagnostic biomarkers in Alzheimer's disease

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Biomarkers will be essential in identifying individuals with prodromal Alzheimer's disease and stratifying participants in clinical trials. In a Policy View in *The Lancet Neurology*, Giovanni Frisoni and colleagues[1] set out the evidence on Alzheimer's disease diagnostic biomarkers, using a framework previously developed in oncology. Their comprehensive review of neuroimaging and CSF biomarkers draws attention to the lack of common standards and clinical validation across health systems, and the subsequent effects on diagnosis. Unless addressed, these variations will limit the ability of the neurological research community to do appropriately powered clinical trials. Thus, to foster standardisation and clinical validation of biomarkers, Frisoni and colleagues present a five-phase strategic research roadmap and note the potential power to increase diagnostic accuracy to be gained from integrating multiple biomarkers; this improvement in diagnostic accuracy can be further augmented by including genetic risk scores.

The successful identification of dozens of risk loci associated with Alzheimer's disease has changed how its pathobiology is viewed but, so far, this knowledge has had little effect on diagnosis, treatment, or prevention. Genomic profiling assesses an individual's unique disease risk, derived from the combined effects of many genetic variants. Since the contributions of genetic variants to the disease risk differ, polygenic risk scores aggregate weighted effect sizes into one metric. For Alzheimer's disease, thousands of genetic risks variants are preselected from those found in large genome-wide studies, capturing the variants that confer the highest risk of disease. Thus, genomic profiling is a promising method to assess risk of progression to Alzheimer's disease in individuals at prodromal or early disease stages. Logistic regression analysis is used to assess the ability of the polygenic score distribution to distinguish people at risk of developing Alzheimer's disease from those not at risk.

The area under the receiver operator characteristic curve (AUC) is the most widely accepted test of prediction accuracy. The AUC statistic of a genomic profile has an upper limit dictated by the disease heritability and prevalence,[2] and high predictive accuracy through genomic profiling can be achieved for diseases with high heritability and low prevalence. The maximum AUC statistic predictive accuracy by genetic profiling in participants form clinical cohorts has been estimated at 82% (for an Alzheimer's disease prevalence of 2%), compared with about 69% based upon estimations using the *APOE* ε4 and *APOE* ε2 alleles exclusively.[3,4] A study by Desikan and colleagues[5] used survival analysis modelling to integrate Alzheimer's disease risk variants and develop a polygenic hazard score for age of onset. The polygenic architecture was found to be an important factor in modifying risk. Together, these findings show a strong genetic component in Alzheimer's disease that can be useful in predicting risk, and hence might be usefully added to neuroimaging and CSF biomarkers to augment their diagnostic abilities.

The expectation is that, as in cancer, comprehensive genomic profiling in Alzheimer's disease will be crucial to select targeted therapies based on the patient's unique risk profile. However, although polygenic risk scoring is a promising approach, genomic profiling for Alzheimer's disease is still in its infancy and should be integrated with other emerging biomarkers to enhance diagnostic accuracy.[6] The ability of genomic profiling to match patients with Alzheimer's disease to targeted therapies also needs to be investigated further. One way of assessing the potential of this approach would be to investigate how well genomic profiling would have stratified responses in previous clinical trials.

A caveat to the use of genetic profiling is that genetic information can be generated at any time in a person's life, potentially long before the onset of disease. The use of genetics to explore disease mechanisms and stratify participants in clinical trials needs to be clearly distinguished from that of estimating the risk of future disease in healthy individuals. Genetic testing for diseases with autosomal dominant inheritance has been available for many years, but it is often not taken up by family members in diseases without interventions that prevent symptom onset and progression. In Huntington's disease, for instance, only

10–20% of family members use genetic testing to know their genetic status.[7] Even in diseases with available interventions, such as inherited forms of breast and colon cancer, genetic testing is not always chosen.[8,9]

Care must be exercised when using genetic information to predict who will develop disease. Precise prediction of Alzheimer's disease susceptibility in an individual is not yet possible, and shifting diagnostic boundaries to include people at risk but without symptoms raises various ethical dilemmas.[10] Even if precision were theoretically possible, individuals might choose not to know their status for a late-life disease, such as Alzheimer's disease. Much work in the communication of genetic risk has been done by clinicians and genetic counsellors, guided by their patients' needs, and this helpful experience can now guide the use of genetic data in common diseases with a heritable component. There are also some challenges to prepare for: the advent of clinical trials including people at risk of Alzheimer's disease but without symptoms and new effective treatments will inevitably bring people forward for genomic risk prediction. These issues require serious consideration by scientists and clinicians working in Alzheimer's disease, particularly when disseminating their research findings.

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