The Lancet Series on Alzheimer's Disease 1

New landscape of the diagnosis of Alzheimer's disease

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Alzheimer's disease involves a drastic departure from the cognitive, functional, and behavioural trajectory of normal ageing, and is both a dreaded and highly prevalent cause of disability to individuals, and a leading source of health and social care expenditure for society. Before the advent of biomarkers, post-mortem examination was the only method available to establish a definitive diagnosis. In this first paper of the Series, we review state-of-the-art diagnostic practices and the typical patient journey in specialist settings, where clinicians engage in a differential diagnosis to establish whether Alzheimer's pathology (cerebral deposition of β-amyloid and hyperphosphorylated tau) is a contributor to cognitive impairment. Biomarkers indicating dysregulation of β-amyloid and tau homeostasis, measured with PET and cerebrospinal fluid analysis, allow a molecular-level diagnosis—a mandatory step in defining eligibility for the recently approved anti-amyloid treatments. We anticipate that easily accessible blood biomarkers, already available in some countries, will lead to a new diagnostic revolution and bring about major changes in health-care systems worldwide.

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Introduction

What is Alzheimer's disease? Depending on who is asked, the answers vary, even among doctors and specialists. The definition of Alzheimer's disease is in dynamic evolution in the expert community, and unanimity has not yet been reached. For all practical purposes, Alzheimer's disease in clinical practice consists of cognitive impairment associated with biomarker evidence of its neuropathological hallmarks: β-amyloid plaques composed of aggregated β-amyloid, and neurofibrillary tangles composed of aggregated tau.[1] Different views on the definition of Alzheimer's disease are addressed in the last paper of this Series.[2] The diagnostic approach and patient journey that we describe in this paper are typical of many memory clinics in Europe and elsewhere[3] and are anchored to the clinical phenotype of a middle-aged or older patient with a history of progressive cognitive decline, sometimes accompanied by behavioural changes, neurological signs, and decreased function in everyday activities. Impairment on cognitive tests, particularly tests of episodic memory, and medial temporal atrophy patterns identified via structural brain imaging might support a clinical–radiological syndromic diagnosis of Alzheimer's disease, but are non-specific as they are shared by other neuropathologies. By contrast, molecular biomarkers, including PET, cerebrospinal fluid (CSF), and blood tests, can specifically mark the presence of β-amyloid-containing plaques and tau-containing neurofibrillary tangles, which are characteristic of Alzheimer's disease, allowing for a clinical–biological diagnosis. These biomarkers enable assessment of neuropathological evidence in vivo, and when used in clinical practice, allow for increased accuracy (90–95%, compared with 60–70% of the traditional purely clinical approach)[4,5] and earlier diagnosis.[6]

It should be acknowledged that frequently, Alzheimer's disease is diagnosed based on clinical investigations and structural imaging only—ie, without biomarker confirmation. However, this is already changing as Alzheimer's disease-specific biological drugs require confirmation of β-amyloid pathology before treatment initiation.[7] At the time of the publishing of this review, the anti-amyloid monoclonal antibodies donanemab and lecanemab[8,9] are approved in an increasing number of countries, including the EU, the USA, the UK, China, Japan, South Korea, Hong Kong, United Arab Emirates, and Israel.

This Series paper on the diagnosis of Alzheimer's disease only considers biomarkers that are currently

Search strategy and selection criteria

We conducted a review of published articles with special focus given towards the past 5 years, since Jan 1, 2020, and up to including March 1, 2025, on the PubMed, Embase, Scopus, and Cochrane databases. The search was restricted to studies published in English with different combinations of the following keywords and medical subject heading terms in PubMed (MeSH) and Embase (Emtree): "Alzheimer's disease", "cognitive impairment", "dementia", "epidemiology", "incidence", "prevalence", "risk factor", "protective factor", "cognitive ageing", "biomarker", "APOE", "patient journey", "workflow", "algorithm", "taxonomy", "mild cognitive impairment", "subjective cognitive decline", "MRI", "PET", "CSF", "amyloid", "tau", "neurodegeneration". We prioritised the most robust evidence from clinical trials, systematic reviews, meta-analyses, and pooled studies. We also reviewed guidelines and position statements from the same period on the diagnosis of Alzheimer's disease, cognitive impairment, and dementia.

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Glossary of terms

Alzheimer's Association Workgroup 2024 Revised Criteria
An integrated biological and clinical staging scheme with six clinical stages (graphically represented in left-to-right columns) and 4 biological stages (top-to-bottom rows). Biological Alzheimer's disease stage and clinical severity are related, but do not travel in lockstep. The typical or average relationship between biology and symptoms can be envisioned as moving along an upper left to lower right diagonal, following the steps of the amyloid cascade (from A–T– to A+T– to A+T+ in the medial temporal lobe, A+T+ with moderate neocortical burden, A+T+ with high neocortical burden. A=β-amyloid, and T=tau pathology). The criteria are conceptual and await validation.

Alzheimer's disease
There is no unanimity on the epistemological definition of Alzheimer's disease, reflected in sets of different diagnostic criteria (Alzheimer's Association Workgroup 2024 Revised Criteria and International Working Group 2024 diagnostic criteria). Disagreements extend to the existence of presymptomatic or preclinical Alzheimer's disease and the interpretation of Alzheimer's disease biomarker positivity in the absence of objective cognitive impairment or deterioration. However, for all practical purposes in clinical practice, Alzheimer's disease can be operationalised as cognitive impairment due to Alzheimer's disease pathology, evolving in stages of increasing cognitive and functional severity.

Alzheimer's pathology
Alzheimer's disease pathology or Alzheimer's disease neuropathological changes consist of the cortical deposition of aggregates of β-amyloid and hyperphosphorylated tau proteins.

Amyloid-targeting therapy
Pharmacological products aimed to decrease the load of aggregated β-amyloid in the brain or prevent aggregation, such as monoclonal antibodies directed towards different forms of aggregated or soluble amyloid. Two of these (lecanemab and donanemab) have been found effective in registration phase 3 trials at reducing cognitive progression by 27% to 39% in patients with Alzheimer's disease operationalised as cognitive impairment and β-amyloid pathology. Tau biomarkers are also ameliorated. Lecanemab and donanemab are approved for clinical use in the USA and other countries.

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.

Braak stages
In Alzheimer's disease, a method to classify the progressive degree of neurofibrillary tangle involvement due to tau pathology. Stages I and II: confined mainly to the transentorhinal region of the brain. Stages III and IV: additional involvement of limbic regions such as the hippocampus. Stages V and VI: additional extensive neocortical involvement.

Cognitive disorders
All conditions that can cause cognitive impairment. These include neurodegenerative conditions such as Alzheimer's disease, but also vascular disease, traumatic brain injury, substance use, infections, disturbances of cerebrospinal fluid dynamics, psychiatric conditions, secondary or reversible cognitive disorders, and more. DSM-5 refers to "neurocognitive disorders" to differentiate the cognitive impairment of psychoses. We believe that the "neuro" prefix does not add meaningful information as, by definition, the brain is the organ responsible for all cognitive disorders.

Cognitive impairment
Problems with thinking, learning, remembering, using judgment, and making decisions that cannot be accounted for by age alone. In the differential diagnosis of cognitive disorders, it is used to infer change from a normal aging trajectory to an abnormal trajectory of decline. In highly educated or performant patients still scoring in the normal range of cognitive tests, clinical judgement can occasionally help identifying those on a trajectory of cognitive decline based on a clear history of progressive and consistent decline.

Delirium
A syndrome of acute confusion due to the direct physiological consequence of medical conditions, effects of psychoactive substances, acute brain diseases, or multiple causes on brain functioning. It often develops on a brain weakened by age-associated or neurodegeneration-associated pathology and usually develops over the course of hours to days with disturbances in attention, awareness, and higher-order cognition. Other neuropsychiatric disturbances are often associated, such as changes in psychomotor activity (eg, hyperactive, hypoactive, or mixed level of activity), disrupted sleep–wake cycle, emotional disturbances, altered state of consciousness, and perceptual disturbances (eg, hallucinations and delusions).

Dementia
A syndrome referring to acquired cognitive impairment affecting disability on daily activities. The term is largely regarded as stigmatising, of limited clinical usefulness (it fails to capture cognitive impairment with no loss of function), and imprecise (singular dementia denotes the syndrome, and plural dementias the diseases and conditions underlying the syndrome). For this reason, while acknowledging that the term is widely used in neurology, psychiatry, and geriatrics, we endorse the terms cognitive impairment and cognitive disorders (see entry in this table). Major neurocognitive disorder is the synonym for dementia in DSM-5.

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International Working Group 2024 diagnostic criteria
Developed for clinical practice and research, the criteria postulate that Alzheimer's disease is a clinical–biological construct consisting of the association of Alzheimer's pathology (brain amyloidosis and tauopathy) with cognitive impairment of specific profiles. Presymptomatic are cognitively unimpaired people who are carriers of fully penetrant autosomal dominant monogenic Alzheimer's disease mutations. Alzheimer's pathology in the absence of cognitive impairment defines the asymptomatic at-risk individuals.

Lewy body disease
A spectrum of conditions due to the accumulation in the central and autonomic nervous system of Lewy bodies and Lewy neurites, whose primary structural component is α-synuclein. The spectrum includes Parkinson's disease (main cerebral affected structure is the substantia nigra), dementia with Lewy bodies (early involvement of the neocortex), and Parkinson's disease dementia (early involvement of the substantia nigra and later of the neocortex).

Mild cognitive impairment (MCI)
A syndrome referring to acquired and progressive cognitive impairment. The person may be slower and less efficient but can still function independently. In older age, it is commonly associated with neuropathology (eg, Alzheimer's disease), but it could be due to anything, including physical and psychiatric conditions. Mild neurocognitive disorder is the synonym to MCI in DSM-5.

Proteinopathies
Refers to certain proteins whose three-dimensional folding conformation becomes abnormal and disrupts cellular function. In Alzheimer's disease and related neurodegenerative diseases, the most frequent are β-amyloid and 3R-4R hyperphosphorylated tau (typical of Alzheimer's disease), α-synuclein (Parkinson's disease, dementia with Lewy bodies, and Parkinson's dementia), TAR DNA-binding protein-43 (TDP-43, in some forms of frontotemporal lobar degeneration), 4R hyperphosphorylated tau (typical of progressive supranuclear palsy and corticobasal degeneration), polyglutamine (Huntington's disease), and superoxide dismutase-1 (SOD1, in some forms of amyotrophic lateral sclerosis).

Staging
In Alzheimer's disease and the dementias in general, staging consists of assigning a degree of severity to the main clinical dimensions of the disease: cognitive, behavioural and psychiatric, functional, and motor or other neurological symptoms. Each should be rated as none, minimal, mild, moderate, or severe. For cognitive or functional staging, the Clinical Dementia Rating Scale is largely used.

Subjective cognitive decline (SCD)
A clinical construct referring to complaints of progressive cognitive problems with formal cognitive testing revealing unimpaired performance. SCD plus refers to certain features of SCD, which increase the likelihood that this condition is related to Alzheimer's disease pathology and that there is a higher risk of objective cognitive decline in the future. The currently proposed SCD plus criteria are: subjective decline in memory irrespective of function in other cognitive domains, onset of SCD within the past 5 years, onset of SCD at 60 years and older, concern (worry) associated with SCD, persistence of SCD over time, seeking of medical help, and confirmation of cognitive decline by an observer.

Worried well
Individuals who do not experience SCD themselves but are concerned about cognitive deterioration or Alzheimer's disease in the future. The label is controversial in the literature as it might lead to genuine concerns or pathology being dismissed.

clinically available or expected to be clinically available within the next year. Biomarkers of β-amyloid plaques and neurofibrillary tangles include PET tracers with high affinity for β-amyloid plaques or pathological tau inclusions in the neocortex,[10] and concentrations or ratios of β-amyloid peptides (Aβ42 and Aβ40) and tau species (including phosphorylated-tau181 [p-tau181]) in the CSF.[11–13] Additionally, some blood tests (p-tau217) reflect the presence of β-amyloid plaques and neurofibrillary tangles, and are now clinically available from several companies in the USA and an increasing number of other countries, but are not yet available globally. Biomarkers of neurodegeneration in Alzheimer's disease include decreased hippocampal and regional cortical brain volumes on structural imaging and reduced temporo-parietal cortical uptake of [^{18}F]fluorodeoxyglucose ([^{18}F]FDG) on PET and neurofilament light in the CSF and blood.

This Series paper shows how these conceptual and technical advances are implemented in the clinical practice of memory clinics in some forerunning countries, and how their experience might be a template for others. This Series[2,14] will adopt the nomenclature proposed by Petersen and colleagues (panel).[15] We will preferentially refer to cognitive impairment and cognitive disorders, and confine use of the term dementia to specifically referring to cognitive impairment associated with impairment in daily activities or when it is part of the current accepted taxonomy (eg, dementia with Lewy bodies). Issues related to the treatment of cognitive and behavioural disturbances in people with Alzheimer's disease are addressed in the second paper of this Series.[14] Controversies related to the very construct of Alzheimer's as a disease and the expected future developments in the field are the subject of the third Series paper.[2]

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Epidemiology in clinical settings

Incidence and prevalence of Alzheimer's disease

Epidemiological studies estimated the incidence of clinically defined Alzheimer's disease dementia (without biomarkers) in Europe to be 3·4 new cases per 1000 person-years at age 65–74 years, with a consistent tripling or quadrupling of incidence every 10 years up to 36 new cases per 1000 person-years at 85 years or older.[16]

The prevalence of all-cause dementia (of which 60–70% is Alzheimer's disease or mixed Alzheimer's disease with other pathologies) was estimated at over 57 million people globally in 2021, with the prevalence set to approximately triple by 2050 due to trends in population ageing, growth, and expected trends in risk factors.[17] Estimates from 2023 set the global number of individuals with biomarker-positive Alzheimer's disease dementia at 32 million, with more than double this number with mild cognitive impairment (MCI) due to Alzheimer's disease pathology (69 million), suggesting that the global prevalence of individuals with cognitive impairment due to Alzheimer's disease is approximately 101 million.[18] Importantly for future prevention studies, the estimated number of cognitively unimpaired individuals with abnormal Alzheimer's disease biomarkers is approximately three times larger than MCI and Alzheimer's disease-dementia cases together (315 million).[18] Future integration of blood biomarkers in population-based studies of the incidence and prevalence of Alzheimer's disease will improve the accuracy of estimates[19] and allow better estimates of incidence and prevalence of mixed forms of dementia (eg, neurodegenerative and vascular), which are increasingly frequent with older age.[20]

Although most studies found that women have a higher prevalence of dementia than men, in part due to longer survival, the weight of biological (sex) and cultural (gender) factors is unclear.[21,22] Stark racial and ethnic disparities have been consistently found in both the prevalence and incidence of dementias, although most evidence comes from the USA, with few additional studies from countries including the UK, Singapore, and China.[23–28] The incidence of all-cause dementia is about 27 cases per 1000 person-years for African Americans aged 64 years and older, compared with about 19 cases per 1000 person-years for White Americans, and about 15 cases per 1000 person-years for Asian Americans.[23] Many of the racial and ethnic disparities in dementia risk can be accounted for by cardiovascular disease risk and social determinants of health: the conditions of the environments where people are born, live, work, and age.[29,30] About 30% of patients with dementia are institutionalised.[31]

Although the overall number of individuals with all-cause dementia is expected to increase, repeated observations have suggested that the age-specific incidence of all-cause dementia in higher-income countries might be decreasing.[32] This decline might be attributable to population-level increases in educational attainment, better control of cardiovascular and metabolic risk factors, and improved socioeconomic conditions.[33–35] These observations indicate that prevention of dementia, including Alzheimer's disease dementia, is not only possible but is currently taking place in high-income countries; similar changes should be promoted in low-income and middle-income countries, where the greatest increment of prevalence is expected in the coming decades.[36] However, more recent modelling of data from the UK has raised concerns about a potential reversal of these positive trends due to an increasing prevalence of unhealthy behaviours such as obesity, sedentary lifestyle, and type 2 diabetes.[37] Decision-makers should be aware that brain health for the community is a fragile state, and positive trends can quickly reverse if not consolidated with appropriate health-care policies and interventions.

For clinic-based studies, the accuracy of the detection of Alzheimer's disease is highly dependent on the diagnostic criteria framework. The use in the same clinical population of the four biomarker-based diagnostic criteria, developed between 2011 and 2021, resulted in 43% of individuals receiving discordant diagnoses, largely due to differences in the weighting of amyloid and tau biomarkers and clinical symptoms.[38] Comparative studies of the two most recent and popular diagnostic criteria are not yet available.[39,40]

Although biomarker-based criteria have the potential to allow a very early diagnosis of Alzheimer's disease in the clinic (biomarkers of Alzheimer's disease pathology are positive long before the development of cognitive symptoms), in practice, diagnosis is often delayed due to structural factors.[41–44] Many patients experience a prolonged interval between symptom onset and formal diagnosis, estimated at around 20–50 months.[41–44] Implementation of blood-based biomarkers together with cognitive screening tests in the primary care system has the potential to help to reduce those delays in some health-care systems.[45]

Risk and protective factors: lifestyle, genetic, and biological

Clinicians can use risk factors to categorise patients into risk strata for targeted secondary prevention interventions. Older age is the strongest risk factor for sporadic Alzheimer's disease,[1] but genetic and non-genetic risk factors also play a role. *The Lancet* Commission identified 14 modifiable factors[46] that might account for 45% of all dementia cases in the general population: lower level of education, hearing loss, hypertension, smoking, obesity, depression, physical inactivity, diabetes, excessive alcohol consumption, traumatic brain injury, air pollution, social isolation, untreated vision loss, and high LDL cholesterol. Other possible risk factors include sleep disturbances and herpes infection.[47–49]

Increases in risk for individuals are modest for most risk factors: risk ratios (RR) range from 1·1 to 2·2,

amounting to 10% to 120% greater risk than the risk-free population.[46] However, the cumulative risk of an individual can be sizable when they carry multiple risk factors.

The *APOE* ε4 allele is the strongest genetic risk factor for non-monogenic Alzheimer's disease: when compared with ε3 carriers, the RR is between 2·5 and 3 for non-Hispanic White ε4 heterozygotes, and between 7 and 10 for ε4 homozygotes, who have a lifetime risk of 40–60%, which is in the range of BRCA1 mutations for breast cancer.[46,50,51] Imaging and fluid biomarkers of brain β-amyloid and tau pathology, and neurodegeneration in cognitively unimpaired individuals, are also associated with risk for dementia and incident cognitive decline.[52,53] Secondary prevention of Alzheimer's disease in cognitively unimpaired individuals at high risk,[54] addressed in the third paper of this Series,[2] leverages on an accurate evaluation of all the above risk factors (for an extended version of this section, see appendix p 12).

Trajectories of normal cognitive ageing and Alzheimer's disease

The earliest event detectable by available biomarkers in Alzheimer's disease is the extracellular deposition of aggregated β-amyloid peptides in plaques (amyloid: A), followed by the intraneuronal deposition of hyperphosphorylated tau in neurofibrillary tangles and neuropil threads (tau: T), synaptic dysfunction and neuronal death (neurodegeneration: N), and, finally, progressive cognitive impairment.[55–57] More details on the neurobiological mechanisms linking the amyloid cascade to clinical dysfunction can be found elsewhere.[58,59]

The A-T-N model is being revised and updated to accommodate the heterogeneity of observed trajectories.[58,60,61] At least three relatively distinct clusters of cognitive trajectories have been identified that differ in frequency, age of onset of pathology, topography of tau pathology and neurodegeneration, clinical phenotype (memory-predominant *vs* non-amnestic), and speed of cognitive decline (figure 1): (1) carriers of autosomal dominant Alzheimer's disease mutations; (2) Alzheimer's disease biomarker positive carriers of the *APOE* ε4 allele; and (3) Alzheimer's disease biomarkers-positive individuals who are not carriers of the APOE ε4 allele. Heterogeneity in the timing and rate of β-amyloid accumulation and the development of cognitive impairment occurring downstream in the amyloid cascade are modulated by stochastic factors such as non-*APOE* genes, non-Alzheimer's disease pathologies, age, sex, lifestyle factors, frailty, and environmental exposures such as literacy, educational attainment, and early life cognitive engagement.[58,60,62–65] Stochastic factors modulate resistance to the development of β-amyloid pathology, or in the presence of β-amyloid pathology, resilience against cognitive decline.[66]

The trajectories shown in figure 1 are critically different from the so-called Jack's curves,[67] for at least two reasons: (1) Jack's curves take a disease-centric approach and represent biomarker trajectories, whereas figure 1 takes a patient-centred approach and represents cognitive trajectories;[2] (2) unlike Jack's curves, figure 1 shows the trajectories of people who never develop biomarker changes and of those who, despite being biomarker positive, never develop cognitive impairment or dementia. This is a key concept when discussing the risk of cognitive impairment and dementia in cognitively unimpaired individuals with risk factors.[2]

Cognitive screening in the general medical practice

Patients presenting to memory clinics differ on average from individuals with cognitive impairment in the general population in that they are typically younger, come from higher socioeconomic backgrounds, are less diverse, have fewer comorbidities, exhibit less severe cognitive impairment, have higher education, and benefit from social and family support that enables access to specialised care.[68]

See Online for appendix

In primary care settings, untargeted cognitive screening is not generally recommended.[69,70] However, targeted cognitive examination in individuals with cognitive complaints is recommended as it improves the diagnosis and care of cognitive disorders.[71,72] The involvement of primary care physicians in the clinical journey of cognitive patients is highly variable among countries.[73] In European countries, before anti-amyloid antibodies were approved, a strong association was found between the authorisation to prescribe traditional dementia drugs (cholinesterase inhibitors and memantine) and pursuing dementia diagnostic work-up in primary care.[73] The availability of

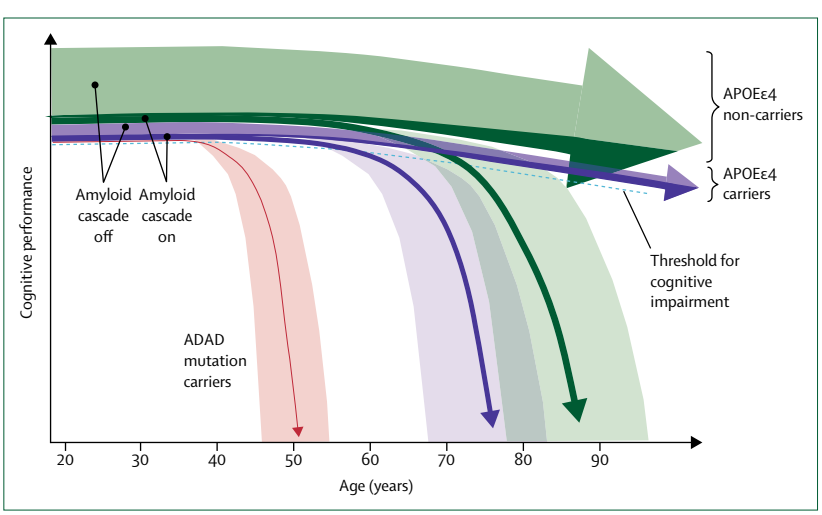

Figure 1: **Cognitive trajectories during ageing by genetic and biomarker status**
Trajectories are those implied by the pathophysiological probabilistic amyloid cascade model of Alzheimer's disease[58] and are consistent with current diagnostic frameworks for Alzheimer's disease.[39,40] Arrows denote cognitive trajectories of autosomal dominant Alzheimer's disease mutation carriers (red), *APOE* ε4 allele carriers (purple), and non-carriers (green). Dark and light colours denote those who enter (on amyloid cascade) and do not enter the amyloid cascade (off). Arrow thickness is roughly proportional to the population prevalence. Red, purple, and green shading around some arrows denote variability within trajectories due to stochastic factors (non-*APOE* genes, non-Alzheimer's disease pathologies, lifestyle factors, frailty, and environmental exposures such as literacy, educational attainment, and early life cognitive engagement). More details in appendix (p 2).

anti-amyloid antibodies might further encourage primary care physicians to direct patients with memory complaints to specialist advice.

In any setting, cognitive examination should always start with history taking, which is a cornerstone in the assessment of people with cognitive complaints.[72,74,75] In Alzheimer's disease, cognitive, behavioural, and functional symptoms develop gradually in a typical pattern. Diagnosis involves gathering detailed history from patients and informants, noting symptom onset, type, and progression, and functional effect. Consideration of comorbidities, medications, laboratory tests, mood, life events, and lifestyle is essential. Self-assessment tools can help to streamline the evaluation process,[76,77] and deviations from the typical course might indicate atypical presentation or other conditions.

History taking should be complemented with a structured cognitive test to assess mental status.[72,74] General practitioners can use a short test such as the Five-Minute Cognitive Test, a combination of the clock-drawing test and a three-item word memory test;[78] the General Practitioner Assessment of Cognition taking 5 min to 10 min;[79] or the more time-consuming (10–15 min) but also more widely used Mini-Mental State Examination (MMSE) or Montreal Cognitive Assessment (MoCA), which is more sensitive to mild cognitive changes.[80,81] When compared with unaided general practitioners' clinical impression alone, short cognitive testing with MoCA almost doubles the number of patients recognised as affected by dementia.[82] The Rowland Universal Dementia Assessment Scale relies less on language and school abilities than MMSE or

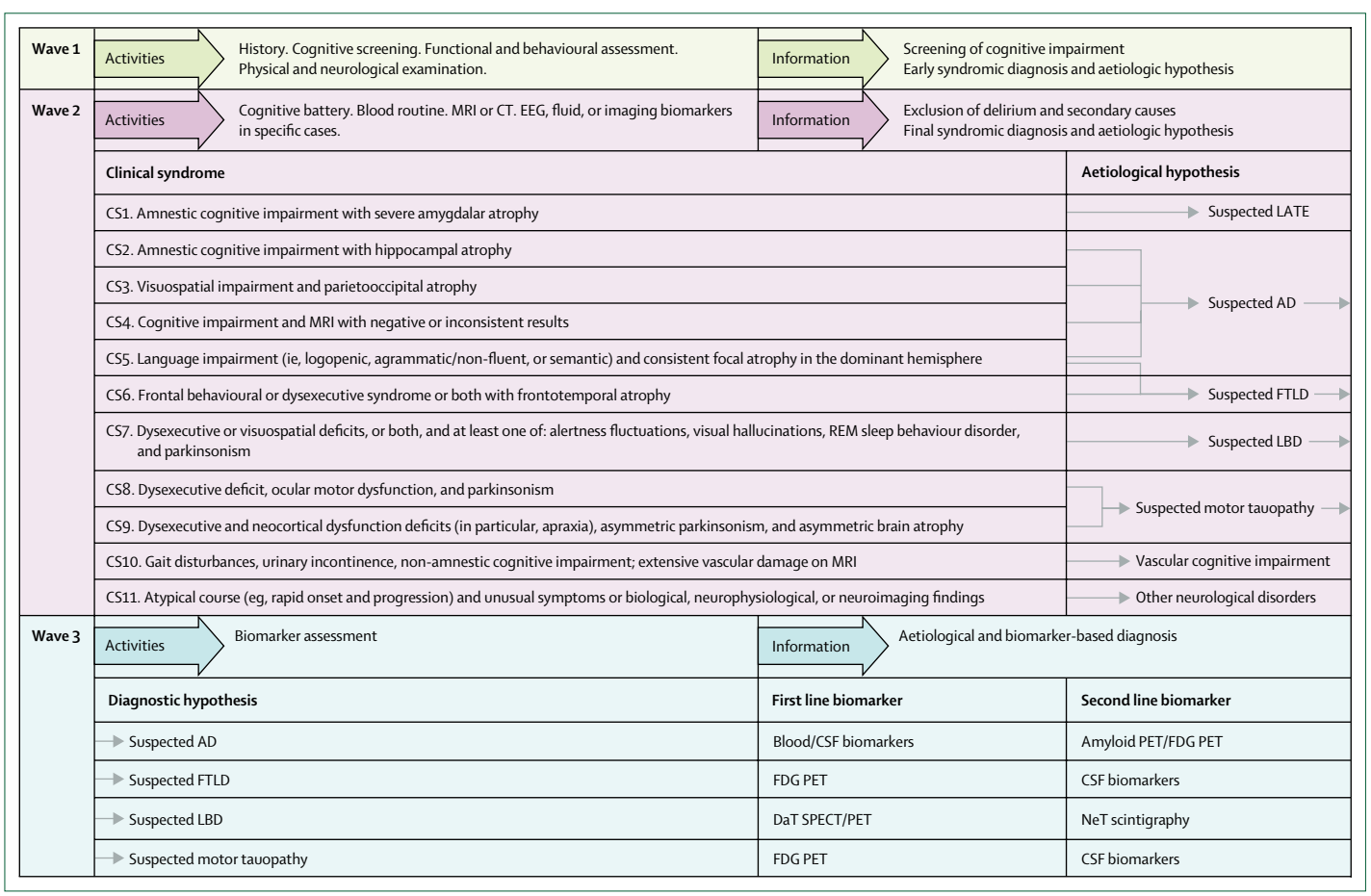

Figure 2: **The patient journey and diagnostic workflow for the biomarker-based diagnosis of Alzheimer's disease and other cognitive disorders in memory clinics**
The workflow is largely the result of a European inter-societal Delphi exercise.[86] Assessment follows three functional waves. Wave 1 is the first memory clinic consultation and allows to provisionally categorise patients into cognitively unimpaired and impaired, perform staging in the latter, identify the most obvious secondary causes, and prescribe diagnostic tests and exams including a cognitive battery. Wave 2 allows the exclusion of less obvious secondary causes, final cognitive staging due to the cognitive battery results, and make a syndromic diagnosis and put forward an aetiological (molecular) hypothesis. Some of the aetiological hypotheses (a, b, c, and d) are confirmed or infirmed in Wave 3 through first-line and second-line imaging and liquid biomarkers. The biomarker-based diagnosis of neurodegenerative conditions can be molecular (only for Alzheimer's disease) or topographical (all others). First-line and second-line biomarkers were selected by 22 experts from 11 European scientific societies with a Delphi procedure.[86] Innovative biomarkers are addressed in the third paper of this Series.[2] More details in appendix (p 4). AD=Alzheimer's disease. CT=computed tomography. CSF=cerebrospinal fluid. DaT=dopamine transporter. EEG=electroencephalogram. FDG=fluorodeoxyglucose. FTLD=frontotemporal lobar degeneration. LATE=limbic-predominant age-related TDP-43 encephalopathy. LBD=Lewy body disease. MIBG=metaiodobenzylguanidine. NeT=norepinephrine transporter. REM=rapid eye movement. SPECT=single-photon emission computed tomography.

MoCA and is commonly used for case identification in culturally and linguistically diverse communities in low-income and middle-income countries.[83] Currently, several digital cognitive tests are being developed and, in the future, could enable broader cognitive testing in primary care and beyond.[84]

Cognitive disorders can be heralded by non-cognitive behavioural symptoms such as apathy, affective symptoms (depression, anxiety), impulse dyscontrol (irritability, agitation), social inappropriateness, disturbances of sleep and vigilance, and psychotic symptoms (delusions, hallucinations),[85] and, especially in the oldest old, non-cognitive motor symptoms such as decreased gait speed and grip strength.[85] Cognitive screening should always be done in these cases,[70] because early stages of Alzheimer's disease pathology can underlie behavioural and motor symptoms even before cognitive impairment overcomes the threshold of complaints.

The patient journey in memory clinics

Although the patient journey might vary across memory clinics, three main functional waves of assessment take place in most memory clinics in high-income countries (figure 2). Depending on local practices and regulations, these assessments can take place over multiple visits and an extended time period or consolidated into fewer visits within a shorter time period.[87,88]

Wave 1

The first step of the journey for patients with cognitive complaints in a memory clinic consists of identifying cognitive impairment through history taking and cognitive screening (figure 2), which is key to interpreting the results of diagnostic biomarkers and for eligibility to pharmacologic treatment.[14,89]

Screening of cognitive impairment

When not done in general practice, cognitive screening takes place early on in the memory clinic with the tests described earlier. In the memory clinics of some of the coauthors of this paper, between 10% and 37% of individuals presenting with cognitive complaints are shown to be cognitively unimpaired based on cognitive testing, with a weighted mean of 13% (figure 3; appendix pp 10–11). These patients are labelled as subjective cognitive decline if they experience and report worsening of cognitive capacities or worried well, if there is a concern of developing impairment in the future, but no complaint at present.[54,90]

Clinicians should be able to recognise whether psychological or psychiatric and medical or neurological conditions underlie their complaints and concerns (eg, sleep problems, longstanding anxiety or depression, personality disorders, physical comorbidity or polypharmacy, or previous stroke), and refer them to the appropriate specialist, if indicated. When none of the above is true, patients with subjective cognitive decline or worried well can be directed to a secondary prevention patient journey, currently under development[54] and addressed in the last paper of this Series.[2]

Wave 2

In patients with cognitive impairment, delirium and non-neurodegenerative causes should be excluded before a neurodegenerative cause can be suspected and a syndromic diagnosis can be made, which will give rise to an aetiological neurodegenerative hypothesis. The pertinent information is collected through functional and behavioural assessment, physical and neurological examination, a cognitive battery, blood routine, and MRI or CT of the brain (figure 2).

Excluding delirium and non-neurodegenerative causes of cognitive impairment

A rapidly progressing cognitive impairment (eg, within days or weeks) indicates delirium (formerly known as acute confusional state; panel). The delirium can be due to non-neurological (eg, electrolyte imbalance, infections, toxic substances, metabolic decompensation, heart failure, or alcoholic encephalopathy) or neurological causes (eg, encephalitis, Creutzfeldt-Jakob disease, cerebral vasculitis, or cerebral amyloid angiopathy-related inflammation), with all conditions requiring urgent evaluation (figure 2).[91,92] Of note, delirium does not rule out an underlying chronic progressive cognitive disorder (so-called delirium superimposed on dementia).[93] Indeed,

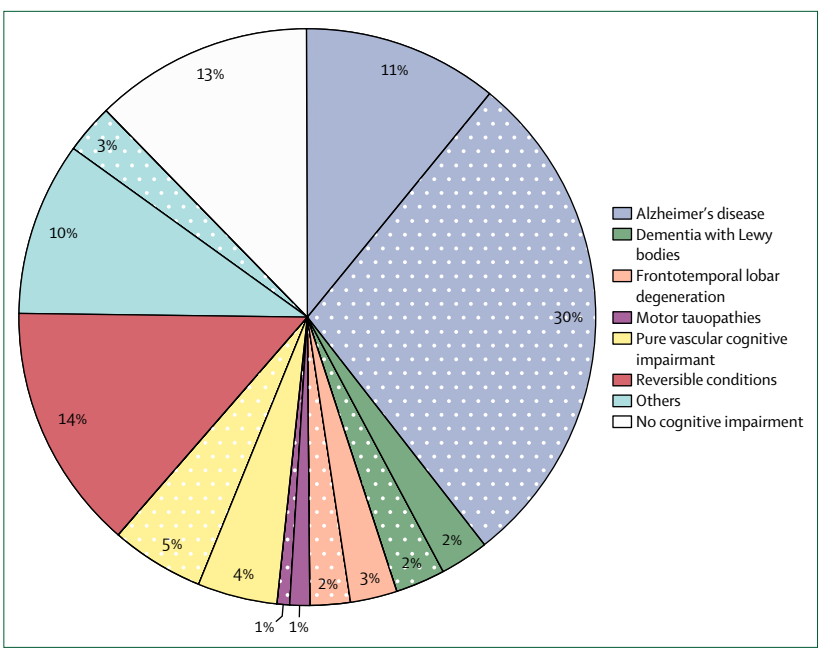

Figure 3: **Taxonomy of patients and use of diagnostic biomarkers at selected memory clinics**
For each colour, cases diagnosed with (dotted) and without (non-dotted) cerebrospinal fluid or PET biomarkers are shown. Based on a survey of 16 526 new consecutive diagnostic patients consulted from Jan 1, 2022, to Dec 31, 2023, in the memory clinics of Amsterdam, Cologne, Copenhagen, Geneva, Lund, Munich, and Paris. Reversible conditions include normal pressure hydrocephalus, meningioma, metabolic conditions, depression. Other section includes low achievement, psychiatric conditions, unsuccessful brain ageing. No cognitive impairment includes subjective cognitive decline, functional cognitive and other psychiatric disorders, neurologic diseases, physical comorbidity, somatic comorbidity, polypharmacy. More details in appendix (pp 10–11).

chronic progressive cognitive disorders increase the risk of delirium (three-fold to four-fold) due to non-neurological causes[94] and 30% of individuals with de-novo delirium develop overt cognitive impairment within 5 years,[95] especially in frail patients.[96] Delirium is twice as frequent in frail patients,[96] who tend to be older than robust patients[65] and feature an increased risk of adverse outcomes. Although no data are available at the moment, it is reasonable to assume that frail patients might not be the prime candidates for treatment with anti-amyloid monoclonal antibodies (addressed in the second paper of this Series).[14] The concept of frailty, its meaning as an indicator of biological as opposed to chronological age, its assessment, and its relevance to cognitive impairment have been reviewed elsewhere.[65] If delirium is identified, the cognitive disorder diagnostic pathway proposed here should be stopped and, if deemed necessary, it can be started again after the delirium episode has resolved.

Information on function in activities of daily living should be assessed by questioning caregivers[97,98] and can be staged into minimal, mild, moderate, and severe disability with the help of structured rating scales.[99] Behavioural and psychological symptoms (agitation, aggression, insomnia, depression, anxiety, hallucinations, and delusions) are generally assessed through an unstructured collection of historical information.[14,70] Staging behavioural and psychological symptoms into minimal, mild, moderate, and severe is also recommended[15] as severity drives treatment. The assessment and treatment of behavioural and psychological symptoms are addressed in the second paper of this Series.[14]

An important question is whether a non-rapidly progressive, non-confusional cognitive impairment is due to potentially curable causes mimicking a neurodegenerative disease, whereby patients could improve with appropriate interventions, such as weaning cognitively impairing medications or treating underlying conditions such as hypothyroidism, depression, or sleep apnoea.[100] These conditions are often detected and managed by primary care providers, but memory clinics should rule out these conditions in the earliest stages of the patient journey (figure 2). Secondary causes of cognitive impairment that should never be disregarded include neurodevelopmental disorders, medical comorbidities, and conditions affecting the white matter. The triad consisting of gait disturbances, urinary incontinence, and non-amnestic cognitive impairment can point to idiopathic normal pressure hydrocephalus or small vessel cerebrovascular disease.[101] MRI of the brain is key to the differential diagnosis, as it can identify lacunes, micro-haemorrhages, superficial siderosis, enlarged perivascular spaces, and extensive white matter changes due to small-vessel disease or cerebral amyloid angiopathy.[102] MRI is also sensitive to detect secondary causes of cognitive impairment, such as subdural haematoma, brain tumours, or idiopathic normal pressure hydrocephalus (figure 2).[86]

Syndromic diagnosis and aetiological hypothesis

In patients with slowly progressive cognitive impairment not due to the conditions mentioned earlier, a neurodegenerative disease should be suspected. Diagnostic reasoning involves defining the clinical syndromic presentation and, if indicated and possible, identifying the underlying molecular pathophysiology.[15] Syndromes are made of cognitive, behavioural or psychiatric, and motor and neurological symptoms, and atrophy patterns (figure 2). The same clinical–radiological syndrome can be due to different pathologies—eg, β-amyloid and tau, α-synuclein, or transactive response DNA binding protein (TDP)-43. However, in general, pathologies are more frequent in some syndromic diagnoses than others, such that syndromic diagnoses drive an aetiological hypothesis of molecular pathology (figure 2).

Cognitive test batteries are combinations of selected neuropsychological tests aimed at clarifying the existence of impairment when screening results are inconclusive and outlining a profile of cognitive impairment. The tests evaluate functions across various cognitive domains—memory, executive function, attention, language, praxis, gnosis, and social cognition—by contrasting individual patient results to age-specific and education-specific population norms.[103] There is no general standard for the definition of impairment, but an outcome of 1·5 standard deviations below the adjusted means for age, sex, and education on normally distributed cognitive test scores, corresponding to about the 95th percentile, is often used in addition to clinical judgment as a threshold between normal and impaired. Below normal cognitive test results, when combined with a history of progressive cognitive decline reported by the patient or, if available, by a reliable informant, are used to infer progressive cognitive decline. Cognitive batteries also enable assessment of the severity of cognitive impairment and can be used to monitor changes over time.

The profile of cognitive impairment across cognitive domains is a major contributor to a syndromic diagnosis. In more than 80% of cases fulfilling the neuropathological diagnosis for Alzheimer's disease, the typical phenotype consists of an amnestic syndrome of hippocampal type, characterised by a low free recall that is not normalised by cueing.[104] This memory profile differs from that observed in most non-Alzheimer's dementias and correlates with Alzheimer's disease pathology.[105] Atypical cognitive presentations of Alzheimer's disease pathology are less frequent and include visuoperceptive, language, frontal, visuospatial, or apraxic changes.

Cognitive profiles are more closely linked to the regional distribution of synaptic dysfunction and neuronal loss (ie, neurodegeneration) than to the specific molecular pathology underlying a neurodegenerative disease. Although certain clinical phenotypes and neurodegeneration topographies are statistically associated with particular molecular pathologies—such as the preferential involvement of the inferior frontal and insular regions in

frontotemporal lobar degeneration with tau pathology (FTLD-tau), the anterior temporal lobe in FTLD-TDP type C, and temporo-parietal atrophy in Alzheimer's disease within the language network—these associations are too weak to be clinically actionable (eg, only ~75% of logopenic variant primary progressive aphasia are underpinned by Alzheimer's disease pathology).[106] Algorithms trying to identify the underlying proteinopathy from a given clinical–radiological syndrome have so far shown poor performance.[107]

Neurodegeneration in Alzheimer's disease is a relatively late event and can be appreciated with specific sequences on structural MRI.[88] Brain CT is less sensitive but can replace MRI when it is not available or contraindicated.[108] Brain atrophy associated with Alzheimer's disease can be differentiated from ageing-associated atrophy as it is more severe and comes in topographic patterns matching cognitive profiles.[109]

Wave 3

In an increasing number of memory clinics, the aetiological hypothesis is confirmed or refuted through biomarker assessment (figure 4). Only biomarkers of β-amyloid, tau, and α-synuclein pathology (in the blood, CSF, and on PET) allow an aetiological diagnosis. Other biomarkers currently in use in memory clinics are biomarkers of neurodegeneration (biomarkers of glucose metabolism on PET, brain dopaminergic denervation on single-photon emission computed tomography, and cardiac noradrenergic denervation on scintigraphy),[86] which allow the presence and topography of synaptic and neuronal loss to be defined more clearly and accurately than atrophy assessment on structural MRI alone or the exploration of specific neurotransmission pathways affected by the degenerative process. Although non-aetiological, this topography-based diagnosis can be used as a proxy, albeit an imperfect one, of the aetiological hypothesis.[111]

We provide here an overview of fluid and imaging biomarkers of β-amyloid pathology, tau pathology, and neurodegeneration that are useful in the clinic and that have been, or will soon be, approved for clinical use by regulatory authorities in the USA and Europe. Research-use-only tests are addressed in the third paper of this

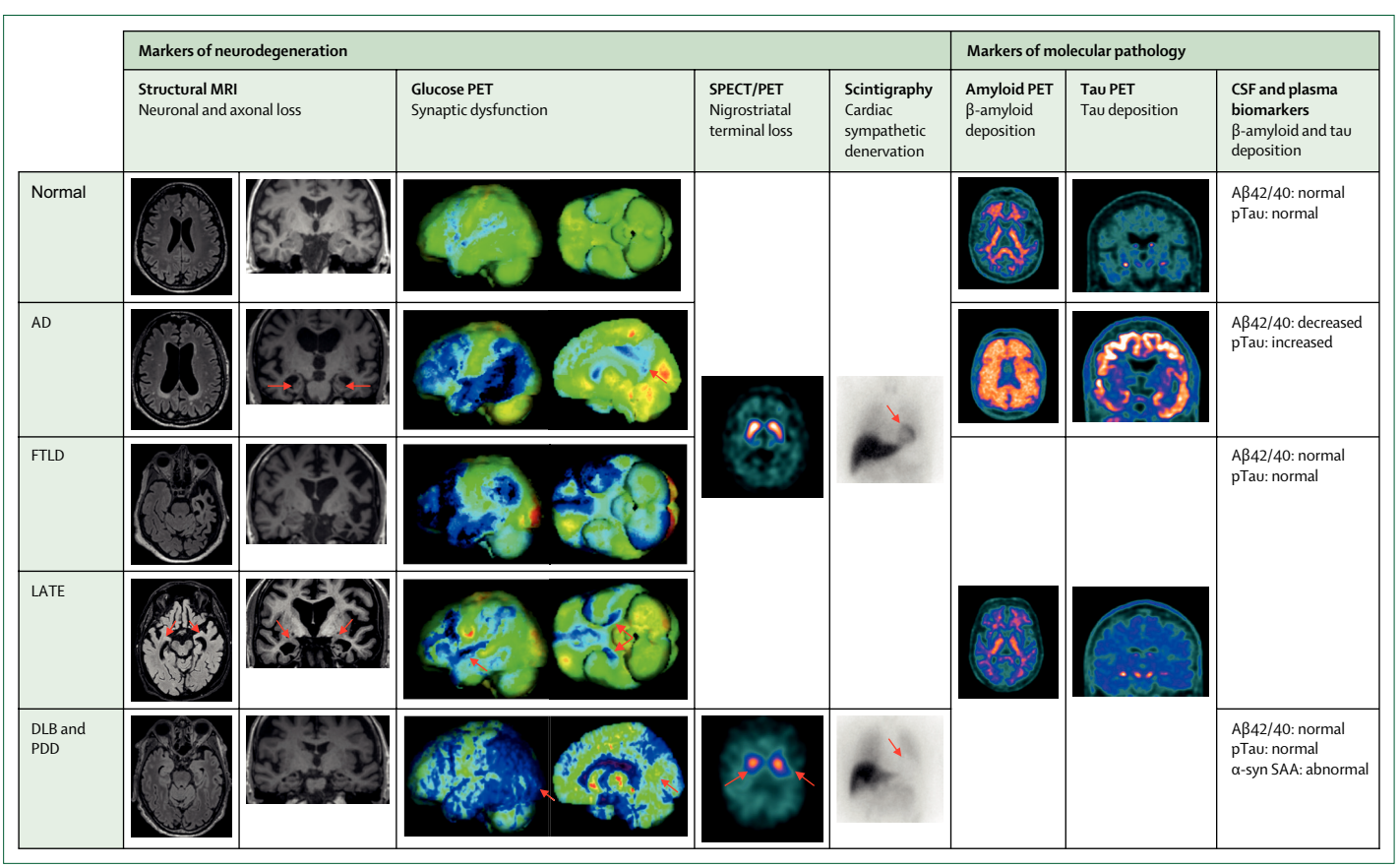

Figure 4: **Typical biomarker profiles across pure pathology neurodegenerative cognitive disorders.**
Blue colour in glucose PET renderings denotes substantial hypometabolism. Orange/red/purple/white colours in nigrostriatal SPECT imaging and amyloid and tau PET denote increased tracer uptake. Images come from the archive of one of the co-authors (VG). More details in appendix (p 8). AD=Alzheimer's disease with typical amnestic phenotype. CSF=cerebrospinal fluid. DLB=dementia with Lewy bodies. FTLD=frontotemporal lobar degeneration with behavioural phenotype. LATE=limbic-predominant age-related TDP-43 encephalopathy.[110] PDD=Parkinson's disease dementia. SAA=seed amplification assay. SPECT=single-photon emission computed tomography.

Series.[2] The ultimate aetiological diagnosis is done through neuropathological assessment, which is not discussed here and can be found addressed in other reviews.[114]

Importantly, PET imaging and fluid markers are not interchangeable. PET reveals the burden of insoluble Alzheimer's disease-related protein aggregates, whereas fluid biomarkers reflect dysmetabolism (altered production or clearance) in soluble biomarkers that are in dynamic equilibrium with insoluble aggregates. The balance of production and clearance of β-amyloid and tau proteins in body fluids (CSF and blood) indirectly reflects the presence of Alzheimer's disease neuropathology. The distribution of insoluble β-amyloid plaques and neurofibrillary tangles can be visualised and quantified via PET imaging, but only once the pathological load reaches concentrations defined as moderate on pathology.[10,39] Notably, fluid biomarkers are more sensitive to the earliest changes in the pathological metabolic pathway than clinical amyloid PET scans, which show a clear signal at the individual level only when pathology burden becomes moderate.[115–117] In contrast to fluid biomarkers, PET informs on both the presence and the topography of pathology, which, in the case of tau PET, correlates with the clinical phenotype.[118]

Biomarkers of β-amyloid pathology

Clinically approved amyloid PET tracers are blood–brain barrier permeable small molecules marked with [^{18}F] (florbetapir, florbetaben, and flutemetamol) that bind with high affinity to β-amyloid plaques and can be detected and mapped by appropriate PET hardware and software. The interpretation of amyloid PET images for clinical purposes is based on standardised visual assessment by physicians who have received formal accreditation.[119] Amyloid accumulation can also be quantified by calculating the relative uptake of the tracer in cortical areas in comparison to a reference region not affected by pathology, most commonly the cerebellum. To allow standardisation across different amyloid PET tracers, a common scale (centiloid) has been proposed, where the values of 0 and 100 represent the anchor points corresponding to a typically normal and a typically pathological PET scan.[120] Positivity to amyloid PET, with appropriate thresholds, allows identifying with high sensitivity and specificity intermediate to high Alzheimer's disease neuropathological changes, associated with intermediate tau pathology (Braak stage ≥III [glossary of terms]).[121]

In the CSF, the accumulation of β-amyloid plaques in the brain parenchyma is preceded by a reduction of soluble Aβ42 peptide relative to the more abundant Aβ40 peptide, resulting in a low Aβ42:Aβ40 ratio.[122–125] The ratios of Aβ42:Aβ40, p-tau181:Aβ42, and total tau:Aβ42 are more strongly associated with β-amyloid pathology than CSF Aβ42 alone,[11–13] and current CSF tests approved by the US Food and Drug Administration (FDA) for Alzheimer's disease use these ratios rather than CSF Aβ42 alone to establish the presence of β-amyloid plaques.[89] When both β-amyloid and tau fluid biomarkers are abnormal, specificity to Alzheimer's disease neuropathology is impeccable, albeit at the expense of decreased sensitivity.[126]

Clinically approved PET imaging and CSF tests for β-amyloid pathology show agreement on the classification of amyloid status in about 90% of individuals.[11,89] Disagreements can occur with a positive CSF test and negative amyloid PET scan, particularly in patients with low amounts of β-amyloid pathology.[127,128] Evidence from large-scale prospective trials shows that both techniques have a relevant effect on diagnostic thinking and clinical management of patients.[129–131] As is the case with many diagnostic tests in clinical medicine,[132] few studies have examined the effects of biomarker testing on patient-related outcomes, with conflicting findings.[133,134]

Biomarkers of tau pathology

At least eight different pathologic variants of misfolded tau have been identified, some of which are associated with relatively specific topography and clinical phenotype such as those of progressive supranuclear palsy and corticobasal degeneration.[135] Similarly to β-amyloid, the tau pathology observed in Alzheimer's disease (3R-4R; panel) can be assessed through PET imaging and CSF measures, and more recently plasma measurements. Tau-PET becomes abnormal when insoluble 3R-4R tau aggregates have already spread into the neocortex.[136,137] Although the topography of β-amyloid deposition is only poorly correlated to the clinical phenotype, the topography of tau evaluated through PET is closely related to cognitive profile[138] and clinical stage.[53,139–142] The visual interpretation protocol, currently approved for clinical use (validated against autopsy), requires a binary interpretation that is restricted to the detection of advanced neocortical tau pathology, corresponding to Braak stages V and VI.[143] Flortaucipir, a first-generation tracer specific to 3R-4R tau aggregates but not to other tauopathies such as progressive supranuclear palsy and corticobasal degeneration, is currently approved for clinical use only in the USA and the EU. However, few centres in the USA and Europe do clinical tau PET scans.

In the CSF and blood, decreased Aβ42/Aβ40 is accompanied by increases in tau species, including phosphorylated tau at positions 181 (p-tau181) and 217 (p-tau217).[122–125] In larger studies, the ratio of phosphorylated to non-phosphorylated p-tau217 (pT217/T217) is a slightly better biomarker of amyloid and tau pathology than the absolute concentration of p-tau217.[124,144] Some medical comorbidities, such as chronic kidney disease, can affect amounts of blood biomarkers including p-tau217 concentrations,[145] and biomarker ratios such as pT217/T217 might mitigate these effects.[146,147] Importantly, p-tau217 and pT217/T217 in the CSF and blood increase early in the natural history of Alzheimer's disease pathology and continue to increase as amyloid and tau pathology accumulate, unlike Aβ42/Aβ40, which decreases early but then plateaus and has lower

associations with tau pathology.[124,148–151] Blood tests for amyloid pathology are clinically available in the USA and a few other countries, including plasma p-tau217 measures with high positive and negative predictive values; these tests can be used early on in the diagnostic journey and can reduce the need for CSF biomarkers and PET scans by approximately 80–90%.[4,149,152–155] The first FDA-cleared blood-based in-vitro diagnostic device for the detection of Alzheimer's disease pathology in patients with symptoms is a ratio of p-tau217 to Aβ42 measured with Lumipulse technology.[155]

Biomarkers of neurodegeneration

Neurodegeneration markers provide the pathophysiological link between the molecular pathology and the clinical phenotype. Synaptic density is the best pathological correlate of the clinical phenotype.[156,157] It is a working assumption in the field that no degree of cognitive impairment can be attributed to Alzheimer's disease—or any other neurodegenerative condition—without some degree of neurodegenerative changes, whether measurable or not. Neurodegeneration markers can support the differential diagnosis between neurodegenerative and non-neurodegenerative conditions. Additionally, the topography of neurodegeneration on MRI contributes to the clinicoradiological syndromic characterisation of patients early in the diagnostic journey (figure 4). Medial temporal atrophy is present in 75–85% of patients with Alzheimer's disease in the mild to moderate cognitive stages, which can be easily appreciated on T1-weighted coronal scans[109] and rated with a simple visual rating scale.[158,159] Additionally, 82% of patients with a behavioural frontotemporal syndromic profile have severe, often asymmetric, anterior frontal or temporal atrophy, or both, on MRI.[109] Severe amygdalar atrophy is typical of limbic-predominant age-related TDP-43 encephalopathy and requires additional specific rating on T1-weighted axial scans.[160]

In the natural history of Alzheimer's disease, atrophy on MRI is a relatively late phenomenon and is often difficult to differentiate from normal ageing or is hardly detectable (Alzheimer's disease with minimal atrophy).[161] Glucose hypometabolism on [^{18}F]FDG-PET is more sensitive to the neurodegenerative process than atrophy on MRI.[162] The detection of grey matter hypometabolism can corroborate the presence of a neurodegenerative disease in uncertain cases, and the topographic pattern of hypometabolism can help to differentiate Alzheimer's disease from non-Alzheimer's disease conditions where molecular biomarkers are not available (eg, frontotemporal lobar degenerations and dementia with Lewy bodies). Excellent reviews on the clinical and biomarker features of non-Alzheimer's disease neurodegenerative conditions are available elsewhere.[163–167]

CSF and plasma neurofilament light are the best-established clinically available fluid biomarkers of neurodegeneration, with increased amounts across neurodegenerative diseases and particularly high amounts in frontotemporal dementia, amyotrophic lateral sclerosis, vascular dementia, and rapidly progressive Alzheimer's disease.[168] In the USA, plasma neurofilament light can be ordered and might have some diagnostic utility, especially in combination with plasma p-tau217, for patients in whom clinicians are considering frontotemporal dementia (higher neurofilament light, lower p-tau217) versus either Alzheimer's disease (lower neurofilament light, higher p-tau217) or dementia with Lewy Bodies (lower neurofilament light, lower p-tau217).[169,170]

Biomarker use in the clinic

Although the biomarker profiles of the most frequent neurodegenerative conditions seen in memory clinics are markedly different when multiple biomarkers are considered (figure 4), reimbursement and logistical considerations typically restrict providers to ordering one biomarker at a time. Appropriate use criteria for amyloid and tau PET have been proposed and recently updated.[171] A Delphi panel of European delegates from pertinent scientific societies has identified first-line and second-line biomarkers with the greatest chance of supporting specific aetiological hypotheses (figure 4). The panellists did not take accessibility and reimbursement into account, which vary across Europe and can profoundly affect the choice of which biomarker to investigate—eg, PET versus CSF testing when the aetiological hypothesis is Alzheimer's disease (figure 2). Similar appropriate use recommendations have been provided for the use of CSF biomarkers.[172] Recommendations for blood biomarkers have also been published,[173] but are currently being updated given advancements in Alzheimer's disease blood tests.

A few notes of caution should be emphasised regarding the interpretation of diagnostic biomarkers in clinical settings. First, particularly in the oldest-old patients, multiple pathologies co-occurring with Alzheimer's disease are the rule rather than the exception,[174] and clinical syndromes and biomarker profiles are sometimes less clear-cut than described earlier. In these cases, it can be difficult to ascertain whether, and to what extent, Alzheimer's disease and non-Alzheimer's disease components contribute to the observed cognitive impairment. This distinction can be relevant in clinical settings where anti-amyloid monoclonal antibodies are available, and an accurate estimate of the contribution of the amyloid cascade to the cognitive phenotype can help to predict the therapeutic success and inform treatment decisions. Importantly, when Alzheimer's disease biomarkers are negative, it is unlikely that Alzheimer's disease pathology underlies the clinical phenotype. Given the increasing frequency of copathology with advancing age, the Delphi panellists contributing to the diagnostic workflow in figure 2 strongly recommended the use of diagnostic biomarkers for individuals younger than 70 years, recommended to consider them based on

individual clinical characteristics in those aged 70–85 years, and did not recommend them in individuals older than 85 years.[86] However, a negative biomarker result is in general a strong argument against a diagnosis of Alzheimer's disease, and particularly in older individuals when Alzheimer's disease pathology is highly prevalent.[175] In general, clinicians should consider repeating biomarker testing if results are discordant with clinical suspicion.

Second, before amyloid targeting therapies were available—and still today in countries where such treatments are unavailable—the value of a biomarker-based diagnosis (whether molecular or topographic) lay in its ability to reduce misdiagnoses, which, in turn, helps to prevent the inappropriate use of cholinesterase inhibitors and memantine in patients with frontotemporal degenerations,[176] and of neuroleptics in patients with dementia with Lewy bodies.[177,178] Moreover, a substantial proportion of patients with MCI or mild dementia assign an inherent value to receiving an accurate diagnosis.[179,180] In the era of amyloid-targeting therapy, however, a biomarker-based diagnosis has become indispensable for identifying patients who might be candidates for anti-amyloid monoclonal antibody treatment—estimated to be between 5% and 17% of memory clinic patients with MCI or mild dementia.[181,182]

Multiple Alzheimer's disease blood tests are clinically available as laboratory-developed tests in the USA and other countries, and must meet technical standards to ensure consistent measurement of the biomarker of interest.[183] So far, only one of the Alzheimer's disease blood tests (Lumipulse p-tau217:Ab42 ratio) has received full FDA clearance. Blood biomarkers of Alzheimer's disease pathology hold promise for improved diagnosis,[184,185] particularly in primary care settings and in low-income and middle-income countries, where cognitive disorders are currently under-recognised, underdisclosed, undertreated, and undermanaged.[186–188]

Most PET, CSF, and blood tests validation studies have been done in primarily non-Hispanic White populations. Racial and ethnic differences in amyloid PET, CSF biomarkers, and blood biomarkers have been reported by some studies but not others.[189–191] Factors such as differential selection effects, rates of medical comorbidities, and prevalence of amyloid pathology might be associated with groups defined by race or ethnicity.[191–193] Therefore, when biomarker tests are done in patients identifying with racial or ethnic groups that have been under-represented in biomarker validation studies, clinicians should interpret the results with a higher level of uncertainty than they would for well represented patient groups, and it might be reasonable to consider a second test in patients with intermediate results.

Finally, in clinicopathological studies, the accuracy of biomarkers is 90% or higher versus moderate and severe Alzheimer's disease pathology burden.[194,195] However, there might be complexities in clinical practice that affect diagnostic accuracy, such as inter-rater variability in classifying amyloid PET status[196] and insufficient uniform measures and cut-offs for both CSF and blood tests.[172,173,197] Some discordance exists between different biomarker modalities and between biomarkers and neuropathology, particularly in individuals with low amounts of amyloid pathology and intermediate biomarker abnormality.[198,199] Given this margin of error, the degree of biomarker abnormality rather than a binary result should be reviewed if available.

Furthermore, the clinician should consider the pretest probability of abnormality for a given patient, as the positive and negative predictive values of any test are affected by the prevalence of the condition of interest in the diagnostic population.[89,200] In the memory clinic diagnostic setting, for example, the positive predictive value of blood biomarkers for Alzheimer's disease pathology will be higher in patients with more severe cognitive impairment than in those with milder cognitive impairment, and vice versa for the negative predictive value.[185] This highlights the importance of clinical phenotyping before interpreting biomarker results.

More details on the differential diagnosis of Alzheimer's disease from other conditions and the diagnostic workflow of figure 2 can be found elsewhere.[86] Importantly, biomarker testing should generally not be done in cognitively unimpaired individuals outside of clinical trials and research studies because the resulting information is currently of uncertain clinical interpretation and non-actionable.[172,173,201]

Conclusions

In this Series paper, we have shown that the theory and practice surrounding Alzheimer's disease and its diagnosis are undergoing dynamic and lively evolution. A better understanding of the natural history of biomarkers associated with Alzheimer's disease pathology has enabled the development of patho-physiologically sensible and clinically useful diagnostic criteria. The increased use of, and experience with, biomarkers in clinical settings has facilitated the development of diagnostic workflows that support earlier, more accurate, and sustainable diagnosis and differential diagnosis of Alzheimer's disease. Advances in the biomarker field have improved the accuracy and structure of diagnostic assessment in all patients, regardless of whether molecular biomarkers are used.

The availability of anti-amyloid monoclonal antibodies in some countries has further accelerated the uptake of diagnostic biomarkers, although the benefits of a timely and accurate diagnostic assessment extend well beyond the indications for monoclonal antibody treatment. Exciting technological advancements have enabled the development of easily accessible blood-based biomarkers, which have already started yet another diagnostic revolution, with radical changes in the diagnostic patient journey in high-income and hopefully soon in

low-income and middle-income countries. The state-of-the-art treatments of cognitive and non-cognitive behavioural symptoms in patients with Alzheimer's disease will be addressed in the second paper of this Series on Alzheimer's disease.[14]

Contributors

GBF drafted the structure of the paper and an early draft of text, tables, and figures. EN was the main contributor to the Epidemiology section. VG was the main contributor to the Wave 3 section and refined figure 4. SES contributed to the Wave 3 section. WMvdF, FJ, and NV contributed to the Cognitive screening in the general medical practice, Wave 1, and Wave 2 sections. All coauthors revised the manuscript at least once, contributed to the literature search, and contributed important intellectual content. Authors appearing on individual papers of the Series contributed to those papers only and had no contribution to the other papers. All authors had the opportunity to read all papers once completed and agree that the paper they co-authored appears in this Series.

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