The Lancet Series on Alzheimer's Disease 3

Alzheimer's disease outlook: controversies and future directions

Giovanni B Frisoni, Emil Aho, Carol Brayne, Olga Ciccarelli, Bruno Dubois, Nick C Fox, Kristian S Frederiksen, Cem Gabay, Valentina Garibotto, Thomas Hofmarcher, Clifford R Jack Jr, Miia Kivipelto, Ronald C Petersen, Federica Ribaldi, Christopher C Rowe, Sebastian Walsh, Henrik Zetterberg, Oskar Hansson

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This is the third in a Series of three papers about the new clinical landscape in Alzheimer's disease. All papers in the Series are available at https://www.thelancet.com/series-do/alzheimers-disease

Memory Center, Department of Rehabilitation and Geriatrics, University Hospitals and University of Geneva, Geneva, Switzerland (Prof G B Frisoni MD, F Ribaldi PhD); Division of Neurogeriatrics, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Stockholm, Sweden (E Aho MSc); Cambridge Public Health, University of Cambridge, Cambridge, UK (Prof C Brayne MD, S Walsh MPhil); Queen Square Multiple Sclerosis Centre, Department of Neuroinflammation, UCL Queen Square Institute of Neurology, Faculty of Brain Sciences, University College London, London, UK (Prof O Ciccarelli MD); NIHR University College London Hospitals Biomedical Research Centre, London, UK (Prof O Ciccarelli); Institut de la Mémoire et de la Maladie d'Alzheimer, IM2A, Groupe Hospitalier Pitié-Salpêtrière, Sorbonne Université, Paris, France (Prof B Dubois MD); Institut du Cerveau et de la Moelle Épinière, UMR-S975, INSERM, Hôpital de la Pitié-Salpêtrière, Paris, France (Prof B Dubois); Dementia

For the first time, reductions in cerebral β-amyloid pathology load and rate of cognitive and functional decline have been achieved in Alzheimer's disease, through pharmacological intervention in randomised controlled trials. However, the results from phase 3 randomised controlled trials of anti-β amyloid monoclonal antibodies are interpreted in different ways, with some experts supporting a clinically meaningful disease-modifying effect, and others judging insufficient benefit-to-risk ratio and opposing market authorisation. In the final paper of this Series, we discuss these contrasting views, all of which wish to contribute to improvements in the quality of life of people with, or at risk of, Alzheimer's disease. We contrast the efficacy, societal costs, and generalisability of monoclonal antibodies for Alzheimer's disease to biologics for other conditions (eg, cancer, multiple sclerosis, and rheumatoid arthritis) and set this debate in the larger context of modern personalised medicine. We discuss current practice implications, future developments directed to β-amyloid and non-amyloid targets that might have more clinical efficacy and less adverse effects for those with the disease, and large-scale prevention interventions for those at risk.

Introduction

Biologics for medical conditions ranging from multiple sclerosis, to some cancers, to rheumatoid arthritis have significantly improved patient care and outcomes. Lecanemab and donanemab are the first monoclonal antibodies with unequivocal evidence of efficacy to reduce cognitive and functional decline in Alzheimer's disease. When applications for a marketing licence were submitted to regulatory agencies, the community of Alzheimer's disease experts showed a wide range of reactions, ranging from lively enthusiasm to strong opposition. Why did this divergence of reactions happen? What is special about dementia, and specifically the Alzheimer's disease field and community, which explains this divergence of reactions? How is it that treatment innovations for other diseases (eg, multiple sclerosis or rheumatoid arthritis), with a similar effect on disability, have been welcomed in such different ways? This Series paper draws on historical, clinical, and scientific considerations to explore why a treatment that has been heralded as a breakthrough by some and received with concern by others.

Anti-β amyloid monoclonal antibodies are not the only major innovation to impact Alzheimer's disease, or expected to do so soon. Drugs active on non-amyloid pathways are being actively explored. Digital biomarkers, which cover measurements of physiology or pathology, for example, through digital health technologies, promise more sensitive and scalable screening compared with current neuropsychological assessment for cognitive impairment. New imaging and fluid biomarkers, including blood biomarkers, have emerged that accurately discriminate the biological changes associated with Alzheimer's disease, paving the way to redrawing the clinical taxonomy of neurodegenerative diseases. Improved knowledge of risk factors has led to the development of pilot secondary prevention programmes for people without cognitive impairment who are at high risk of Alzheimer's disease.

Search strategy and selection criteria

We searched PubMed, Embase, Scopus, and Cochrane for articles published from Jan 1, 2020, to March 1, 2025. 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", "anti-amyloid", "monoclonal antibodies", "lecanemab", "donanemab", "symptomatic", "disease-modif*", "amyloid-related imaging abnormalities", "ARIA", "clinical* meaningful*", "discontinu*", "APOE", "oncology", "cancer", "biologics", "rheumatoid arthritis", "disability", "morbidity", "quality of life", "disease-free survival", "progression-free survival", "cost-effectiveness", "health care", "burden of disease", "multiple sclerosis", "DALY", "disability-adjusted", "costs", "biomarkers", "secondary prevention", and "primary prevention". 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. Biologics for early stage breast cancer (trastuzumab), lung cancer (pembrolizumab), multiple sclerosis (ocrelizumaba), and rheumatoid arthritis (tocilizumab) were chosen based on the availability of randomised clinical trials using endpoints homologous to the prevention of disability in Alzheimer's Disease. No filter was set based on cost, efficacy, and safety.

Finally, the lexicon in Alzheimer's disease can be confusing; therefore, this Series[1,2] adopts the nomenclature proposed by Petersen and colleagues.[3] Specific terms are presented in the first paper of this Series.[1] Here, we will preferentially refer to cognitive impairment and neurocognitive disorders, and confine the use of the term dementia to when specifically referring to cognitive impairment associated with impairment in activities of daily living or when it is part of current accepted taxonomy (eg, dementia with Lewy bodies).

The context

Historical context

Alzheimer's disease was first described in 1906[4] and was so called by Kraepelin in 1910. It was only in 1976 that Robert Katzman stipulated that Alzheimer's disease and senile dementia were a single process and should, therefore, be considered a single disease—describing Alzheimer's disease as a major killer.[5] This reframing paved the way for Alzheimer's disease research through the decade of the brain (from 1990 to 1999) to modern research on the disease.[5] In those early years, and still today in many memory clinics, people with cognitive disorders in high-income countries were diagnosed and managed with low-technology approaches and low-cost tools,[6,7] including neuropsychological tests, sometimes a CT scan, traditional knowledge of geriatrics, and often inappropriate use of psychotropic drugs.[8,9,10] It took 17 years from Katzman's[5] seminal paper for the first symptomatic drug to be developed and reach the market (ie, tacrine, a cholinesterase inhibitor, in 1993). Tacrine production was soon discontinued due to substantial hepatic toxicity, and was replaced by the cholinesterase inhibitors donepezil, rivastigmine, and galantamine, authorised for clinical use since 1996, and the partial NMDA receptor antagonist memantine, authorised in 2002. The phase 3 trials of cholinesterase inhibitors and memantine showed cognitive benefits in patients with dementia who received treatment. These results were interpreted as delaying progression of cognitive impairment and disability by about 6 months (in the context of a clinical natural history spanning over 10 years).[11] This interpretation initially led to the widespread prescription of cholinesterase inhibitors and memantine, but increasing scepticism about their clinical impact grew in the following years.

In 2016, the French High Authority for Health stated that the medical benefits of cholinesterase inhibitors and memantine were "insufficient to justify their reimbursement by national health insurance schemes".[12] De-reimbursement took place in France in 2018, allowing the country to save €90 million per year on drugs.[13] France was followed by Albania and Latvia, but the national health systems in all other European countries continued to reimburse or provide these drugs. The debate about the use of resources for patients with Alzheimer's disease became even more intense when, in the early 2010s, new and expensive biomarkers, such as PET β-amyloid, became available for a disease that many still considered untreatable.[14,15]

Monoclonal antibodies and blood biomarkers

Differences in assessment of the contemporary evidence base have only grown since 2021, with the highly controversial accelerated approval of aducanumab by the US Food and Drug Administration (FDA), based on efficient removal of β-amyloid plaques as a surrogate endpoint in two phase 3 trials—of which only one showed some signal of benefit on clinical outcomes.[16] After the equivocal results of aducanumab, lecanemab and donanemab gave proof of a clear and replicable signal of modification of the cognitive and functional trajectories of patients with Alzheimer's disease in large and appropriately designed trials.[17,18] Although both treated and untreated patients' cognition deteriorated over the 18 months of the trials, the treated patients had, on average, a milder decline.[2] Lecanemab and donanemab have received traditional approval by the FDA and other health authorities based on efficacy on clinical outcomes. Importantly, when anti-β amyloid monoclonal antibody trials are considered as a whole (ie, trial outcome *vs* average amyloid PET response in the trial), a direct correlation is present between β-amyloid plaque removal and the degree of slowing of cognitive decline.[19] Between 3% and 6% of trial participants who received treatment showed brain oedema or haemorrhages that resulted in symptoms.[2] In the placebo-controlled phases and open-label extensions, four of the 1612 participants treated with lecanemab[20] and five of the 2031 participants treated with donanemab died.[21] Of these treatment-related deaths, one participant was treated with tissue plasminogen activator and the other with anticoagulants, prompting warnings of a potentially lethal interaction of the drugs with anticoagulant and thrombolytic therapy.[18,20] The long-term outcomes of the 10–18% of patients with asymptomatic treatment-related brain oedema or haemorrhages are not known.[2]

Monoclonal antibodies come at a time when another major opportunity is advancing in maturity for Alzheimer's disease. In specialist settings, blood biomarkers to measure Alzheimer's disease pathology (Aβ42-to-Aβ40 ratio [Aβ42/40] and tau phosphorylated at Thr 217 [p-tau217]) have entered clinical practice in an increasing number of countries (eg, the USA, Japan, the UK, and China) to assist diagnosis. These measures have been shown to have good agreement with PET imaging, cerebrospinal fluid (CSF) biomarkers, and post-mortem diagnosis.[22,23] Several p-tau217 blood tests can predict brain PET amyloid status as well as, or better than, CSF tests.[24,25] Research assays in the blood have now been adapted to high-throughput clinical pathology platforms[26] and are available for clinical use in the USA and several other countries.[24] These blood tests are now

Research Centre, Department of Neurodegenerative Disease, UCL Queen Square Institute of Neurology, University College London, London, UK (Prof N C Fox MD); **UK Dementia Research Institute at UCL, University College London, London, UK** (Prof N C Fox); **Danish Dementia Research Centre, Department of Neurology, Copenhagen University Hospital–Rigshospitalet, Copenhagen, Denmark** (K S Frederiksen MD); **Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark** (K S Frederiksen); **Division of Rheumatology, Geneva University Hospitals and Geneva Centre for Inflammation Research, Faculty of Medicine, University of Geneva, Geneva, Switzerland** (Prof C Gabay MD); **Laboratory of Neuroimaging and Innovative Molecular Tracers, Geneva University Neurocenter and Faculty of Medicine, University of Geneva, Geneva, Switzerland** (V Garibotto MD); **Division of Nuclear Medicine and Molecular Imaging, Geneva University Hospitals, Geneva, Switzerland** (V Garibotto); **Center for Biomedical Imaging, Geneva, Switzerland** (V Garibotto); **IHE – The Swedish Institute for Health Economics, Lund, Sweden** (T Hofmarcher PhD); **Department of Radiology, Mayo Clinic, Rochester, MN, USA** (Prof C R Jack Jr MD); **Karolinska Institute, Division of Clinical Geriatrics, Center for Alzheimer Research, Karolinska Institutet, Stockholm, Sweden** (Prof M Kivipelto MD); **University of Eastern Finland, Institute of Public Health and Clinical Nutrition, Kuopio, Finland** (Prof M Kivipelto); **Ageing Epidemiology Research Unit, School of Public Health, Imperial College London, London, UK** (Prof M Kivipelto); **FINGERS Brain Health Institute, Solna, Sweden** (Prof M Kivipelto); **Department of Neurology, Mayo Clinic, Rochester, MN, USA** (Prof R C Petersen MD); **Department of Molecular Imaging, Austin Health and Florey Department, University of Melbourne, Melbourne, VIC, Australia** (Prof C C Rowe MD);

Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, Sahlgrenska Academy at the University of Gothenburg, Mölndal, Sweden (Prof H Zetterberg MD); Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden (Prof H Zetterberg); Department of Neurodegenerative Disease, UCL Institute of Neurology, University College London, London, UK (Prof H Zetterberg); UK Dementia Research Institute at UCL, University College London, London, UK (Prof H Zetterberg); Hong Kong Center for Neurodegenerative Diseases, InnoHK, Hong Kong Special Administrative Region, China (Prof H Zetterberg); Wisconsin Alzheimer's Disease Research Center, University of Wisconsin School of Medicine and Public Health, University of Wisconsin-Madison, Madison, WI, USA (Prof H Zetterberg); Centre for Brain Research, Indian Institute of Science, Bangalore, India (Prof H Zetterberg); Department of Clinical Sciences Malmö, Faculty of Medicine, Malmö, Sweden (Prof O Hansson MD*); Memory Clinic, Skåne University Hospital, Lund, Sweden (Prof O Hansson MD)

*Contributed to this manuscript from the inception of the Series in May, 2024, until November, 2024 when the first version was ready to submit. Once he was employed by Eli Lilly on November 26, 2024, he had no access to any subsequent manuscript versions or revisions and did not contribute to the project any further

Correspondence to: Prof Giovanni B Frisoni, Memory Center, Department of Rehabilitation and Geriatrics, University Hospitals and University of Geneva, 1205 Geneva, Switzerland
giovanni.frisoni@unige.ch

being validated in primary care and real-world settings.[27] Although it has been known for over two decades that Alzheimer's disease pathology antedates clinical symptoms by about 10–20 years,[28,29] the availability of scalable diagnostic tests and drugs active on Alzheimer's disease pathology creates the potential for, and opens the question of, screening for pathology in people without cognitive impairment.

Debate in the field

Epidemiological data at the population level have provided the driving rationale for substantial research investments in Alzheimer's disease and other cognitive disorders. However, the impressive developments in the detection and treatment of Alzheimer's disease, where cognitive impairment is attributable to the amyloid cascade,[2] have not come with similar advancements for the much larger segment of older people (>80 years) with Alzheimer's disease and who have cognitive impairment due to multiple factors (ie, combinations of neuropathologies including Alzheimer's disease, physical diseases, and psychosocial factors). This knowledge gap has led to a separation of dialogues between physicians seeing patients in primary care hospital wards who are older and have cognitive impairment, and those seeing younger patients with cognitive impairment, with purer neurodegenerative conditions, in neurological and specialist clinics. The prospect of rapid changes in the management of the younger patient population raises concerns that the older patient population might be neglected and left behind. This is at the heart of much of the debate discussed in this Series paper.

Three approaches can be discerned in the community of experts, with parallels to the general medical literature,[30] all aiming to give meaningful answers to patients with cognitive impairment and Alzheimer's disease (table 1). The diverging views stem from different priorities given to traditional and acknowledged elements of medical knowledge and praxis; namely, disease mechanisms, patient care and allegiance, and community wellbeing. Although not necessarily mutually incompatible, each has a different set of implications, benefits, potential harms, and costs to society that will be discussed. Sections on the disease-centred, patient-centred, and population-centred approaches were drafted by advocates of the three approaches (CRJ disease centred; BD patient centred; and CB and SW population centred).

Disease-centred approach

The biological approach to Alzheimer's disease is based on the concept that the disease is defined by its unique neuropathology (β-amyloid plaques and tau neurofibrillary tangles). Thus, the detection of intermediate to high Alzheimer's disease pathology by accurate and disease-specific biomarkers is equivalent to diagnosing the disease. The disease exists on a continuum that begins with the appearance of biomarkers of Alzheimer's disease pathology in asymptomatic individuals. The disease progresses biologically during the preclinical period, and when a sufficient pathological burden is reached, symptoms appear and then progress. Cause and effect mechanisms exist; the disease causes symptoms, not vice versa.

Disease-specific biomarkers (ie, core biomarkers) of Alzheimer's disease can be divided into two broad categories. Pathophysiological biomarkers[36] or core 1 biomarkers are β-amyloid PET, approved CSF assays of Aβ42/40, tau/Aβ42, p-tau/Aβ42, and accurate plasma p-tau assays. These biomarkers change early in the disease course, remain atypical throughout the disease course, and are usually used for diagnosis. Topographical, downstream[36] or core 2 biomarkers, such as tau-PET, reflect tau proteinopathy, change later in the disease course, and are best used for staging and prognosis.[33]

A common misperception around core 1 biomarkers is that they only indicate the presence of β-amyloid plaques and, therefore, because a diagnosis of intermediate or high Alzheimer's disease pathology requires both plaques and tangles, an atypical core 1 biomarker does not represent Alzheimer's disease pathology more generally. Core 1 biomarkers cannot detect mild disease pathology. An atypical core 1 biomarker represents intermediate to high disease pathology more than 95% of the time in symptomatic individuals and 74–87% of the time in asymptomatic individuals.[33,37] Therefore, diagnosing Alzheimer's disease by an atypical core 1 biomarker is consistent with the classical neuropathological definition of Alzheimer's disease—β-amyloid plaques and neurofibrillary tangles—in most cases.

The biologically based approach operates from the assumption that symptoms due to Alzheimer's disease reflect damage to or loss of the neuropil. By the time an individual becomes symptomatic, extensive and irreversible neuronal loss has already occurred. The optimal timepoint in the disease course to intervene therapeutically is as early as possible, to avoid or delay irreversible neuron loss. This approach is taken in every other area of medicine where diseases can be detected before the onset of symptoms. At present, however, no disease-targeted interventions have been approved for asymptomatic individuals and, until this occurs, biomarker testing in this population should be reserved for observational research and clinical trials.[33,38]

Patient-centred approach

The medical act is built on the allegiance between patient and physician under the common assumption of beneficence and non-maleficence.[30] Better health of the community is achieved by upscaling this approach to the population. Incomplete or missing pathophysiological knowledge of disease mechanisms or treatment interventions (eg, serendipitous treatment discoveries),

is acceptable as long as the evidence indicates health-related quality of life improvements.

The bidirectional and honest communication of information between patient and physician is key to a fiduciary relationship and allows patient engagement into treatment, which in turn is key for optimal care. Communicating a diagnosis evokes disease narratives in the patient's imagination and different diagnostic labels

	Disease centred	Patient centred	Population centred
Specificities			
Core goal	To identify and accurately measure in vivo mechanisms that cause cognitive impairment	To address patients' needs	To improve the health of the whole population
Scientific discourse	Understanding disease biology will enable development of disease-specific biomarkers and disease-modifying treatments; disease-modifying treatments for individuals will contribute to improvement of population health	Any intervention to improve the quality of life of patients is acceptable, regardless of the depth of understanding of their biological effect	Dementia is a multifactorial syndrome most commonly affecting people who are older than 80 years; a significant impact on population health can be achieved through interventions relevant to large strata of the population with, or at risk of, dementia
Knowledge source	Observational cohorts with in vivo deep phenotyping (clinical, biomarkers, genetics, and pathology) that span the continuum of Alzheimer's disease, from preclinical to cognitively impaired stages	In specialised care knowledge comes mainly from the disease-centred literature; in general practice knowledge comes mainly from the population-centred literature	Population-representative cohorts
Definition of Alzheimer's disease	Alzheimer disease is a biological construct; the disease is defined by its unique neuropathology; the disease begins before the onset of symptoms; the disease is assumed to cause symptoms	Alzheimer's disease is a clinical–biological construct; the disease starts with the first symptoms; diagnostic labels should reflect shared physician's and patient's narratives	Alzheimer's disease pathology is frequent in people without dementia, and most people with dementia have mixed pathologies; Alzheimer's disease as a distinct, homogeneous disease entity is rare in the general population
Diagnosis of Alzheimer's disease	Via biomarkers of Alzheimer's disease pathology	Via clinical assessment and biomarkers of Alzheimer's disease pathology	Via clinical assessment; biomarker assessment in subgroups of the general population to assess risk
Interventions for Alzheimer's disease	Drugs against Alzheimer's disease pathology and symptomatic drugs	Symptomatic drugs, drugs against Alzheimer's disease pathology, and psychosocial interventions	Interventions on social determinants and prevention of modifiable risk factors
Efficacy of anti-β amyloid monoclonal antibodies	Monoclonal antibodies remove plaque, but do not eliminate the Alzheimer's disease pathophysiological process; the earlier they are taken, the more effective they are	Monoclonal antibodies are a partially effective but relevant, therapeutic strategy contributing to delay of the progression of cognitive deficits and disability	Monoclonal antibodies have a small clinical effect in few selected patients at enormous social costs that will deflect resources from those at greater need
Commonalities			
Aim of clinical research on Alzheimer's disease and other cognitive disorders	Improving the cognitive health and quality of life of individuals and the community	As for previous column	As for previous column
Role of co-pathology	Alzheimer's disease pathology incompletely explains cognitive impairment in many individuals who are older (>85 years). Alzheimer's disease pathology is common in those who do not develop cognitive impairment and co-pathology is increasingly prevalent with older age (vascular lesions, α-synuclein, or TDP-43, among others); although significant levels of neocortical tau pathology are associated with progression to cognitive impairment, a proportion of individuals with Alzheimer's disease pathology never develop cognitive impairment within their lifetimes; increasing co-pathology increases likelihood of cognitive impairment	As for previous column	As for previous column
Role of brain reserve	Genetic, brain vascular, environmental, and social factors can significantly modulate the phenotypic expression of Alzheimer's disease pathology	As for previous column	As for previous column
Biomarker use	At present, biomarkers should not be used in people without cognitive impairment outside the context of observational or therapeutic research studies because no treatments have yet been approved for this population	As for previous column	As for previous column
Indication for anti-β amyloid monoclonal antibodies	People with Alzheimer's disease at the mild cognitive impairment or mild dementia stage	As for previous column	In tax-funded health systems, these drugs are unlikely to be considered cost-effective and, therefore, should not be rolled out
Contraindication for anti-β amyloid monoclonal antibodies	Patients at moderate or severe stages, with medical contraindications, or with comorbid brain pathology where Alzheimer's disease seems clinically unlikely to be the major cause of impairment; these patients should receive mainly supportive and psychosocial care	As for previous column	As for previous column

(Table 1 continues on next page)

	Disease centred	Patient centred	Population centred
(Continued from previous page)			
People with cognitive impairment and positive Alzheimer's disease biomarkers	Drugs directed against Alzheimer's disease pathology including anti-β amyloid monoclonal antibodies could, when shown to be effective, be used to reduce the risk of incident cognitive impairment and dementia; the indication will depend on an overall assessment of co-occurring risk factors and absolute risk	As for previous column	The drugs would need to be part of a screening programme for which the evidence clearly meets the established WHO criteria,[31] including net population benefit and cost-effectiveness
Health-care delivery model	Interventions for individuals and the community should be developed in synergy to improve general health and quality of life	As for previous column	As for previous column

The caricatured profiles are intended to clearly differentiate between different perspectives on addressing the Alzheimer's disease conundrum.[32] Disease-centred,[33] patient-centred,[34] and population-centred[35] approaches aim to help the field answer complex questions and nuanced, and heterogeneous views exist within and across these perspectives. Views on appropriate use of biomarkers and drugs are based on current knowledge and should be updated as new evidence accumulates. More information on anti-β amyloid monoclonal antibodies can be found in the second paper of this Series.[2] Alzheimer's disease pathology includes brain deposition of β-amyloid plaques and tau neurofibrillary tangles.

Table 1: **Paradigmatic approaches to solving the Alzheimer's disease conundrum**

evoke different narratives. The lay narrative of Alzheimer's disease is that of an untreatable condition leading invariably to profound disability and loss of personal dignity.[39] The label of Alzheimer's disease should be reserved for individuals with cognitive impairment and positive biomarkers of disease pathology, as these individuals will, almost invariably, deteriorate cognitively and functionally.[40]

Appropriately designed studies are not available, but some indicate that a man aged 65 years with positive amyloid biomarkers and no cognitive impairment has an approximately 20–40% lifetime risk of developing cognitive impairment.[41,42] This approach is akin to that of the biological criteria for Huntington's disease, where people with 36 to 39 CAG repeats are considered at high risk of developing the phenotype, but are not regarded as affected by the disease.[43] On the other hand, individuals with evidence of both β-amyloid and tau pathology in the neocortex have a much higher risk compared with isolated brain amyloid of developing cognitive impairment and, pending confirmatory studies, are good candidates for the label of presymptomatic Alzheimer's disease.[34]

Medical care should be equitable and affordable, but decisions on resource allocation are in the domain of politics rather than clinical medicine. Physicians should acquire the resources necessary to meet the interests of the individual patient, regardless of the impact that such actions might have on others who might also have a need. The concept of balancing rights cannot be part of the physician's conceptual framework as it would never be in the patient's best interest. Physician-scientists should advocate their patients' need for resources by offering politicians meaningful and reliable data to back their decisions on balanced resource allocation.

Population-centred approach

A population-centred, or public health, approach synthesises evidence from various disciplines. The cornerstone of this approach is epidemiology, the scientific discipline concerned with the measurement of disease-changing rates over time and understanding differential risk between population groups. Public health approaches incorporate this measurement with biological understanding of the disease and its societal context to prioritise finite resources, maximise benefit across groups, and reduce health inequities.

The correlation between cognitive impairment and Alzheimer's disease pathology is relatively weak.[44–46] Harmonised neuropathological data from six population-based cohorts show that most cognitive disorders, including Alzheimer's disease, are associated with mixed pathologies and this is increasingly true in people older than 85 years.[47] In a cross-sectional analysis of US and UK autopsy cohorts, 85% of those with severe Alzheimer's disease pathology had at least one additional neuropathology.[48] Further, most people with Alzheimer's disease pathology do not develop cognitive impairment in their lifetime.[41,42,48] These observations challenge the concept of Alzheimer's disease as a definable, pathologically based disease entity,[49] and population-based studies often consider the dementia syndrome in its entirety, rather than trying to neatly differentiate between clinical labels of different cognitive disorders.

Risk of cognitive impairment is unevenly distributed across society, with those with low socioeconomic status being at greater risk compared with those with higher socioeconomic status of developing cognitive disorders, including Alzheimer's disease, and typically spending more of their lives with the condition.[50,51] Socioeconomic determinants of greater risk include built environment, housing quality, poverty and income inequality, educational and occupational opportunities, and broader societal factors, like structural racism and sexism—the environments in which people live, work, and grow old. Public health approaches balance the need for clinical interventions to support those acutely in need (secondary and tertiary prevention), with investments in prevention that address these determinants (primary and primordial prevention) so that future generations accumulate less risk.[52]

The population-centred approach is a powerful lens through which the disease-centred and patient-centred approaches can be placed in the broader societal context. This approach integrates evidence regarding early detection and screening with interventions agreed by society to be appropriate for people with cognitive disorders. Interventions should be placed in the context of future need, ensuring intergenerational fairness. Recognising the complexity of these challenges, the population-centred approach acts as a framework to bring together evidence from epidemiology and clinical medicine, alongside social science disciplines, health systems research, public policy and health economics, and ethics among other disciplines.

Common ground

Despite the declared epistemological and technical differences and the occasionally heated debate,[53] the three approaches also have many relevant commonalities, summarised in table 1. Of these, co-pathology and brain reserve deserve particular attention.

The frequent co-occurrence of other pathologies with Alzheimer's disease, and the weak correlation between Alzheimer's disease pathology and cognitive severity, especially in adults aged 85 years or older, are often cited by proponents of a population-centred approach as reasons to question the validity of defining Alzheimer's disease as a distinct pathological entity, except in rare, early onset cases. A third key argument is the observation that environmental (eg, high education) and social factors (eg, lively social network and high socioeconomic status) can protect from the phenotypic expression of Alzheimer's disease pathology (ie, brain resilience).

The disease-centred approach does not deny observations of co-pathology and brain resilience. Instead, it asserts that the clinical penetrance of Alzheimer's disease pathology can be better appreciated by breaking down the disease pathology into severity stages. Early evidence with tau-PET in convenience cohorts shows that people without cognitive impairment with advanced tau pathology might have a high (around 70–75%) 6-year risk of incident cognitive impairment,[54,55] suggesting that beyond a given disease pathology stage, the beneficial impact of brain resilience might be overcome. The modulating role of brain resilience and co-pathology is acknowledged by the recently revised diagnostic and staging criteria for Alzheimer's disease, representing the manifesto of the disease-based approach.[33]

Brain resilience represents a key conceptual point of contact between the different perspectives.[56] Advances in blood-based biomarkers of Alzheimer's disease and other pathologies will allow for the accurate measurement of the clinical penetrance of Alzheimer's disease pathology in diverse cohorts representative of the general population and with long follow-up, in turn allowing for the indirect estimation of the weight of co-pathology and brain reserve. Early testing of brain resilience and co-pathology in clinical cohorts seem to suggest their significant modulatory role on clinical penetrance in patients with Alzheimer's disease pathology.[57,58] When substantiated in larger and more varied cohorts, the different positions outlined here might reconcile around the very essence of scientific debate: empirical evidence. In the meantime, the debate on the possibly major contentious issue, ie, the approval and marketing of monoclonal antibodies, could benefit from insight on the use of homologous drugs in conditions bearing some analogy with Alzheimer's disease.

Lessons from other diseases

Clinical efficacy of biologics for oncology, multiple sclerosis, and rheumatoid arthritis

Lecanemab and donanemab reduced progression by 0·45 points and 0·70 points, respectively, versus placebo over 18 months on a global cognition and disability scale (Clinical Dementia Rating Sum Of Boxes, CDR-SB), representing 27% and 36% decline reduction, respectively.[17,18] Time-to-event analyses showed slightly lower effects, with 25% of patients receiving lecanemab and 33% receiving donanemab showing no disease progression.[17,18] Clinically serious adverse events related to treatment occurred in one in 300 patients and one in 65 patients, respectively.[17,18] Efficacy and adverse events are discussed in the second paper of this Series.[2]

Monoclonal antibodies have been used for over 25 years in conditions other than Alzheimer's disease, and many questions relevant to their use for Alzheimer's disease have been answered. To inform the debate on approval, marketing, and use of monoclonal antibodies for Alzheimer's disease, we contrast disability endpoints of monoclonal antibodies for Alzheimer's disease with those in high-incidence cancers (breast and lung cancer), a neurological condition with low incidence (multiple sclerosis), and a non-neurological condition with low incidence (rheumatoid arthritis). These conditions differ from Alzheimer's disease in age profiles, natural history, patient-related outcomes beyond disability, and adverse effects, so any analogy should be cautious.

Oncology

Oncology was the first domain for biologics in the clinic,[59] initially for advanced stages, due to improvements in progression-free survival and overall survival by a few months to a year.[59] The cancer-specific endpoint most similar to CDR-SB is progression-free survival. In advanced lung cancer, when compared with chemotherapy pembrolizumab increased progression-free survival from 6·0 months to 10·3 months, and 6-month survival from 72% to 80% (figure 1).[61] Serious adverse events occurred in 27% of individuals treated with pembrolizumab

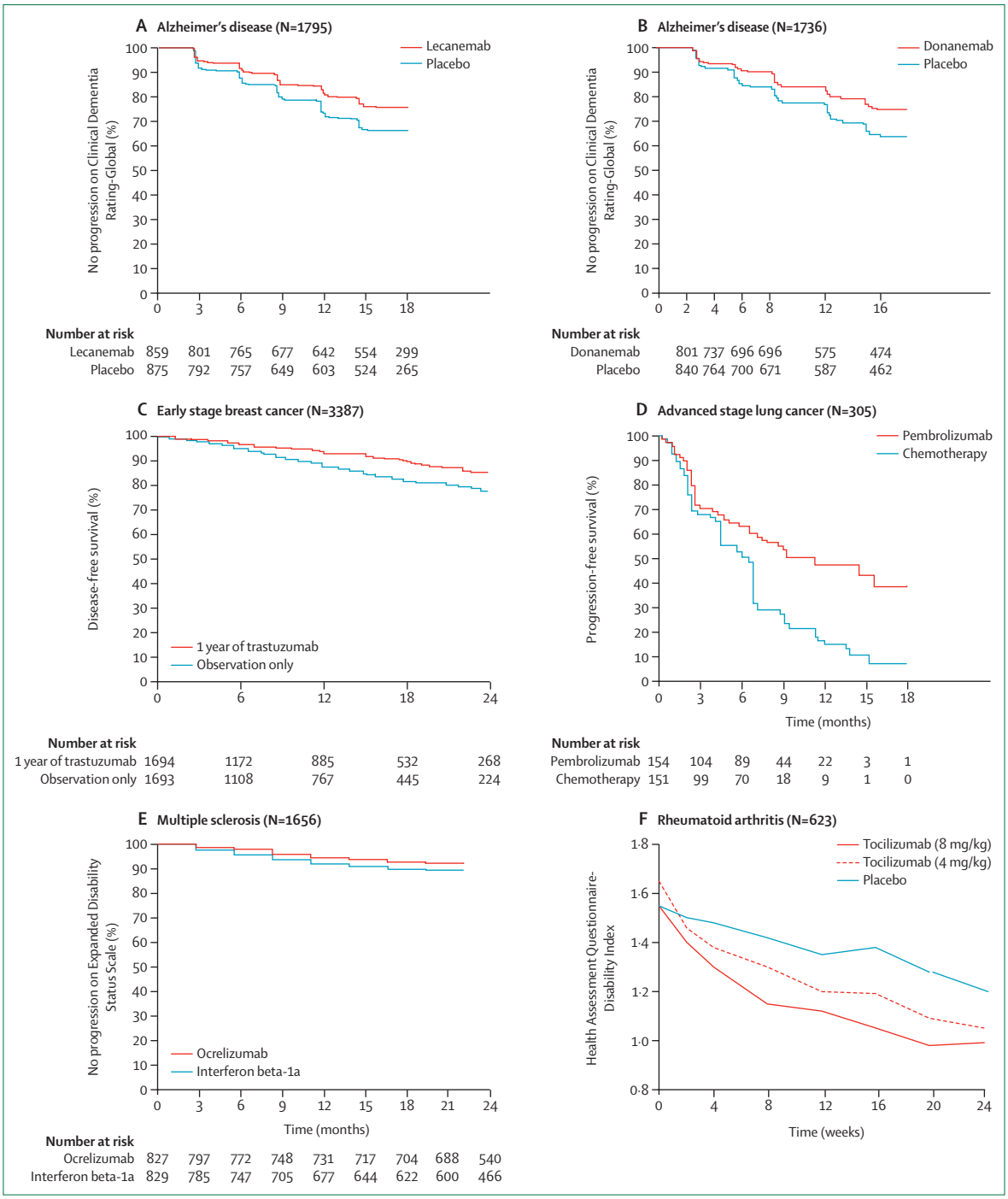

Figure 1: **Effect of monoclonal antibodies in Alzheimer's disease, cancer, multiple sclerosis, and rheumatoid arthritis**
All panels show time-to-event data except for tocilizumab, where mean scale values are shown. Group sizes at the start of the observation period are shown at the bottom of each graph except for tocilizumab. Curves are taken from the original publications and redrawn for consistency of the y-axis scale except for tocilizumab due to copyright regulations. (A) Reproduced from van Dyck and colleagues,[17] with permission from the Massachusetts Medical Society. (B) Reproduced from Sims and colleagues[18] with permission from American Medical Association. (C) Reproduced from Piccart-Gebhart and colleagues[60] with permission from Massachusetts Medical Society. (D) Reproduced from Reck and colleagues,[61] with permission from the Massachusetts Medical Society. (E) Reproduced from Hauser and colleagues,[62] with permission from the Massachusetts Medical Society. (F) 566 of 623 participants completed the study. Reproduced from Smolen and colleagues.[63] The Clinical Dementia Rating-Global is a 0-to-3 scale version of the Clinical Dementia Rating scale, where levels are 0, 0·5, 1, 2, and 3, and extreme values have similar meaning to the Clinical Dementia Rating-Sum of Boxes. More details on the Clinical Dementia Rating-Sum of Boxes, progression-free survival, disease-free survival, Expanded Disability Status Scale, and Health Assessment Questionnaire-Disability Index can be found in the appendix (p 2).

See Online for appendix

versus 53% with chemotherapy.[61] In early stage breast cancer, trastuzumab increased disease-free survival from 77% to 86% at 2 years, and overall survival from 73% to 79% at 12 years. Disease-free survival in the comparator group was 73% at 2 years and overall survival was 79% at 12 years.[60,64] Serious adverse events were reported in 8% of those who received trastuzumab versus 4% in the observation group. One death of 154 treated patients was attributed to pembrolizumab,[61] and one death of every 280 patients treated with trastuzumab.[60]

Multiple sclerosis

Disability in multiple sclerosis can be stepwise, relapse related, or progressive relapse independent.[65] The main endpoints are relapse prevention and disability delay. Treatments like ocrelizumab, ofatumumab, ublituximab, and rituximab lower relapse rates by 46–59% compared with placebo or standard of care.[62,66–68] The impact on disability is modest compared with placebo or standard of care, with incidence reduced from 10·5% to 6·9% with ocrelizumab, and from 29% to 17% with natalizumab (figure 1).[62,69] In primary progressive multiple sclerosis, the benefit on disability progression is even less, from 36% to 17% in untreated versus treated groups.[70] Monoclonal antibodies for multiple sclerosis are generally well tolerated, but natalizumab can cause progressive multifocal leukoencephalopathy in 0·9% of patients, with 25–30% mortality.[71,72] JC virus (Polyomavirus hominis 2) antibody testing can inform on progressive multifocal leukoencephalopathy risk.[72]

Rheumatoid arthritis

Disability in rheumatoid arthritis results from inflammation-related structural joint damage. Early use of disease-modifying antirheumatic drugs (DMARDs) like methotrexate improves prognosis and long-term outcomes. Clinical trials in patients with incomplete response to methotrexate show that biological DMARDs combined with methotrexate are superior to methotrexate alone for remissions and function (figure 1). The incremental benefit of IL-6 receptor inhibitors tocilizumab (figure 1) and sarilumab on disability at 24 weeks is around 0·20–0·25 Health Assessment Questionnaire Disability Index points, close to the minimal clinically relevant change.[73] Overall, biologics improve physical function more than conventional DMARDs, with a standardised mean difference of 0·44 (95% CI 0·38–0·50) in the health assessment questionnaire.[74] Serious infection rates at 12 months for patients treated with abatacept, rituximab, and tocilizumab range from 4·7 to 8·1 per 1000 people per year.[75] Reactivation of latent tuberculosis has been seen with anti-TNF monoclonal antibodies. Rare cases of intestinal perforation have been reported with tocilizumab versus other rheumatoid arthritis treatments (2·7 *vs* 0·2–0·6 per 1000 people per year).[76]

Contrasting the efficacy of biologics for Alzheimer's disease and other conditions

Overall, the aforementioned observations suggest that the reduction in disability from monoclonal antibodies in Alzheimer's disease is similar in magnitude to homologous drugs in breast and lung cancer, multiple sclerosis, and rheumatoid arthritis. In these conditions, biologics also impact clinical endpoints, like relapses, and recurrence, which do not occur in Alzheimer's disease. Biologics are also significantly more expensive than non-biologic drugs, costing between US$50 000 and $200 000 annually per case (table 2). Severe adverse events, including death, occasionally occur during treatment with biologics for cancer, multiple sclerosis, and rheumatoid arthritis, but preventive strategies have been developed. Although increased survival is clearly a valuable outcome, a priority for many families of patients with Alzheimer's disease and society is to reduce time spent with severe disability.

One criticism of monoclonal antibodies for Alzheimer's disease treatment concerns the limited generalisability of current trial results from highly selected, homogenous groups to the broader population with Alzheimer's disease.[77] This issue is common across many medical domains,[78,79] including cancer, multiple sclerosis, and rheumatoid arthritis, where trial participants often have fewer comorbidities, higher socioeconomic status, and less-diverse ethnicity than patients in routine clinical practice.[80,81] Alzheimer's disease research faces similar challenges of diversity and external validity, especially given the older age of Alzheimer's disease patients, who often have mixed neuropathology, comorbidities, and frailty.[82]

Another criticism is that if monoclonal antibodies are reserved to those meeting strict trial criteria, only a small proportion will benefit.[77] It has been estimated that, with trial-like eligibility criteria, only 8–15% of patients with early stage Alzheimer's disease would qualify for monoclonal antibody treatment in real-life settings.[83,84] In comparison, biologic usage in breast cancer is higher than it was when biologics started to be used (30–40% of patients), after more than 25 years of experience and seven drugs in clinical use;[59,85–87] for multiple sclerosis, usage was 36% of patients before 2017,[88] and 74% of patients in 2020, after 20 years of experience and 15 disease modifiers in clinical use;[89] and for rheumatoid arthritis between 10% and 75% of patients in different countries[90] and seven monoclonal antibodies in clinical use for the past 25 years.[91] However, since most people with Alzheimer's disease at the mild cognitive impairment stage in the community are unidentified even in high-income countries such as the USA[92,93] and they twice outnumber those with dementia,[94,95] potential candidates for monoclonal antibodies in memory clinics could be significantly higher than current statistics suggest.[96] Based on CSF biomarker data from Sweden, around 5·9 million individuals in Europe and 2·2 million individuals in the USA could be eligible.[97]

The comparative societal burden of Alzheimer's disease

The previous section suggests some comparability of the impact on delaying disability or analogous outcomes of biologics across Alzheimer's disease, cancers, multiple sclerosis, and rheumatoid arthritis. Decision makers and payers should interpret these observations, based on highly selected clinical populations of small size, within the broader context of societal disease burden, and take into account disease prevalence, incidence, years of life lost, years lived with disability, costs, and the expected effects and value drivers of treatment (table 3). Alzheimer's disease accounts for about 70% of all dementia cases,[100] and a large proportion of patients is undiagnosed.[92,93] Due to scarcity of available information on the societal burden specific to Alzheimer's disease, in the following analysis we have included all dementias, recognising that it only in part reflects memory clinic patients eligible for monoclonal antibodies.

The dementias typically affect older (>65 years) individuals, with an average of 2·5 life-years lost per case—lower than conditions affecting younger (<65 years) people, like multiple sclerosis (7·8 life-years lost per person; table 3). Rheumatoid arthritis also affects younger (<65 years) people, but has low mortality effects. The quality of life lost due to disability (years lived with disability) for an individual patient with dementia is 1·2 years (table 3), lower than multiple sclerosis (7·7 years) and rheumatoid arthritis (2·4 years), but higher than cancer (0·3 years). Due to their high prevalence, dementias have the highest global burden of years lived with disability (1·5-times higher than cancer and five-times higher than rheumatoid arthritis; table 3).

The estimated global cost of all dementia cases is about US$1·3 trillion[101]—similar to Spain's gross domestic product. In Europe, the cost per incident case of multiple sclerosis is about ten-times higher than dementia, mainly due to longer disease duration (table 3). Although the total disease burden (disability-adjusted life-years lost, the sum of years of life lost, and years lived with disability) for dementias are seven-times lower than cancer, total dementia costs in Europe are nearly 40% higher than all

	Alzheimer's disease	Alzheimer's disease	Early stage breast cancer	Lung cancer	Multiple sclerosis	Rheumatoid arthritis
Drug features						
Drug	Lecanemab[17]	Donanemab[18]	Trastuzumab[60]	Pembrolizumab[61]	Ocrelizumab[62]	Tocilizumab[63]
Cost per year, US$	26 500	32 000	63 592	196 588	78 858	51 272
Sociodemographics						
Age, years	71*	73*	49*	65†	37*	51*
Sex, female	52%	57%	100%	39%	66%	65%
Decline analysis						
Scale	Clinical Dementia Rating Scale-Sum of Boxes	Clinical Dementia Rating Scale-Sum of Boxes	Disease-free survival	Progression-free survival	Multiple Sclerosis Functional Composite	Health Assessment Questionnaire-Disability Index
Crude progression rate per year	0·30	0·46	NA	NA	0·05	0·42
Effect size	0·19	0·26	NA	NA	0·20	0·25
Time-to-event analysis						
Event	No progression of disability or cognitive impairment	No progression of disability or cognitive impairment	Disease-free survival	Progression-free survival	No progression of disability on Expanded Disability Status Scale	NA
Length of follow-up, months	18	18	24	18	24	6
Events in treated	76%	74%	86%	39%	93%	NA
Events in comparator	68%	64%	77%	7%	89%	NA
Efficacy at time-to-event	8%	10%	9%	32%	4%	NA
Number needed to treat	13	10	11	3	25	NA
Safety						
Adverse events	Serious ARIA-E	Serious ARIA-E	Severe congestive heart failure	Serious treatment-related adverse events	Any serious adverse event	Serious infections or infestations
Rate	0·3%	1·5%	0·5%	21·4%	6·9%	3·0%

Outcomes and related metrics are disease specific. For details on calculation of the data see the appendix (p 2). NA=not applicable as time-to-disability analyses are not available. ARIA-E=amyloid-related imaging abnormalities with cerebral oedema or sulcal effusion. *Mean. †Median.

Table 2: **Efficacy of anti-β amyloid monoclonal antibodies to delay clinically meaningful outcomes and serious adverse events**

	Alzheimer's disease and other dementias	All cancer	Multiple sclerosis	Rheumatoid arthritis
Epidemiology				
Median incident age (5-year groups), years	75–79	65–69	30–34	50–54
Global prevalence, million cases	57 (49–65)	85 (81–89)	1·9 (1·7–2·1)	18 (16–20)
Global incidence, million cases per year	9·8 (8·6–11·2)	24 (22–25)	0·06 (0·06–0·07)	1 (0·9–1·1)
Life-years lost				
Per incident case, years	2·5	10·4	7·8	0·7
Total, million	25 (6–64)	244 (229–261)	0·49 (0·47–0·51)	0·72 (0·61–0·83)
Years lived with disability				
Per incident case, years	1·2	0·3	7·7	2·4
Total, million	12 (8–15)	8 (6–10)	0·48 (0·34–0·63)	2·4 (1·6–3·2)
Disability-adjusted life years				
Per incident case, years	3·7	10·7	15·5	3·1
Total, million	36 (17–77)	252 (236–269)	1·0 (0·8–1·1)	3·1 (2·3–4·0)
Cost of disease in Europe, €				
Cost per incident case, millions	0·21	0·07	2·05	0·37
Annual cost per patient	35 772	13 948	51 543	18 265
Total cost per year, million	442 182	318 150	37 490	56 823
Distribution of costs, €				
Pharmaceuticals	17 145 (4%)	51 165 (16%)	Not specified	4549 (8%)*
Direct medical costs	39 050 (9%)	112 853 (36%)	13 636 (36%)	24 391 (43%)
Direct non-medical costs	149 330 (34%)	Not included	11 728 (31%)	Not included
Productivity loss	Not included	111 949 (35%)	12 126 (32%)	18 979 (33%)
Informal care	236 657 (54%)	42 183 (13%)	Not included	8903 (16%)

Data are estimates (95% CI), unless otherwise specified. Data are from the 2021 Global Burden of Disease study.[98,99] Estimates should be interpreted in light of the diversity of sources across countries and health and social care systems. Not included indicates that a cost component is excluded from the reference. Not specified indicates that the cost component is unavailable at a specified disaggregated level. Index can be found in the appendix (p 4). *Only biological treatment.

Table 3: **Global burden and cost of disease**

cancers, indicating a disproportionate economic impact of dementia compared with its health impact. WHO estimates that the condition responsible for the largest increase of disability-adjusted life-years between 2000 and 2019 is dementia, with expectations for further rise.[102]

Importantly, about 90% of dementia costs in high-income countries are from direct informal care and non-medical expenses, with medical costs comprising only about one-sixth of expenses and pharmaceutical costs being negligible (table 3). This pattern differs dramatically from cancer, multiple sclerosis, and rheumatoid arthritis, where medical costs are 30–50% of total costs. If the 5-month progression delay seen with lecanemab in clinical trials over 18 months[103] can be replicated in a clinical population and maintained over several years, substantial cost savings could result. The cost of dementia increases sharply with severity, with an approximately €25 000 annual difference between mild and severe stages.[104] Delaying progression to more severe stages could lower costs and free up time for caregivers, but might only delay higher costs later.

As with cancer, multiple sclerosis, and rheumatoid arthritis,[105–107] higher severity involves increased diagnostics, treatment, and monitoring costs. Considering these factors, monoclonal antibodies for Alzheimer's disease could be cost-effective if drug prices and delivery costs are substantially reduced from current levels (table 2).[108,109] However, real-world data on eligibility for monoclonal antibody treatment, responsiveness, long-term clinical effects, adverse events, survival, and associated costs are necessary to substantiate this. If cost savings can be shown, families might benefit most.

Cost-effectiveness calculations should also account for differing health-care funding models. In many countries, long-term care is financed separately from health care. Although payers for long-term care might see benefits, health-care payers might face an unsustainable impact at current prices. For instance, EU treatment costs for lecanemab could exceed €133 billion annually if priced like in the USA, representing over half of the EU's pharmaceutical budget.[96]

Health-care systems capacity will also face challenges.[110] Although most focus has so far been on dementia costs, there are twice as many patients with mild cognitive impairment[94,95] and who could be potential candidates for monoclonal antibody treatment. At least in the early stages of treatment approval, pressure from patients and families

might overwhelm memory clinics' diagnostic capacity, which is critical for treatment eligibility. Primary care could, in due time, take on some of this burden, helped by the privileged longitudinal relationships with patients, a holistic view of health, and team-based care models.[111]

Moving forward: diagnosis, treatment, and prevention of Alzheimer's disease

Innovative biomarkers: Fluid and PET

A biomarker with great applicative potential is blood NF-L, an axonal cytoskeleton protein released during axonal and neuronal injury. An established disease-monitoring biomarker in multiple sclerosis,[112] NF-L is also a sensitive measure of neurodegeneration across conditions.[113] The lack of specificity of NF-L makes it potentially useful for screening and monitoring neurodegenerative diseases.[114]

Plasma p-tau217 is as accurate to detect β-amyloid pathology as clinically approved CSF tests, and even superior for tau tangle pathology.[24] The detection accuracy of p-tau217 in primary and secondary settings exceeds 90%,[27] drastically reducing misdiagnoses in primary and secondary care.[27] Dual-threshold approaches can decrease the use of CSF and PET markers by 80–85%.[27,115] Diagnostic performance varies with disease stage and pretest clinical probability,[25,116] emphasising the importance of thorough clinical and cognitive assessments. In memory clinics, high Alzheimer's disease prevalence results in high positive predictive value, but in primary care, lower prevalence lowers the positive predictive value and increases false positives. Thus, thresholds should be adjusted accordingly, or test positivity viewed as a risk marker, rather than a definitive diagnostic test.[27] Implementation will vary regionally based on health-care governance models.[116–118]

CSF MTBR-243 changes in late disease stages[119,120] and might be used to exclude patients with advanced tau pathology unlikely to respond to amyloid monoclonal antibodies.[18] Blood concentrations of endogenous fragments (endogenously cleaved MTBR-243), alone or with other p-tau species like tau phosphorylated at Thr 205, might detect both disease state and stage.[120–123] WHO is establishing global standards for Alzheimer's disease blood tests.[124]

Differential diagnoses with Alzheimer's disease include dementia with Lewy bodies and cognitive impairment of Parkinson's disease (due to misfolded α-synuclein), and frontotemporal degeneration (usually due to TDP-43 and pathological tau isoforms).[125–127] α-Synuclein and TDP-43 often co-occur with Alzheimer's disease pathology[126,128,129]and are associated with faster progression and poorer drug response.[127,130–134] Misfolded α-synuclein can be detected via seed amplification assays in CSF with accuracy around 90%.[135] Skin biopsies might replace CSF testing in some patient groups.[136] TDP-43 in extracellular blood vesicles is being studied,[137] but protocols require standardisation.[138] Fluorinated PET tracers for α-synuclein ([^{18}F]ACI-12589 and [^{18}F]C05-05, and [^{18}F]SPAL-T-06) and TDP-43 ([^{18}F]ACI-19626) are in early validation stages,[139–142] which will help to understand the impact of co-pathology on disease course and response monoclonal antibodies.

Neuroinflammation, mainly due to astrocytic and microglial activation, might be a key pathophysiological determinant and an interesting diagnostic target.[143] Fluorinated PET tracers targeting astrocytic and microglial translocator protein (TSPO) show increased cortical signal in Alzheimer's disease. Fluorinated PET tracers weak signal impairs clinical usefulness,[144] and some suggest that TSPO might not be an appropriate target.[145,146] Newer tracers for MAO-B in reactive astrocytes ([^{11}C]deprenyl and [^{18}F]SMBT-1) show increased signal early in the disease course,[147,148] correlating with markers of astrocyte activation like GFAP and YKL-40,[149–151] but contrasting findings have also been reported.[152] Pathology-specific radiolabelled bispecific antibodies allow sufficient brain entry for PET imaging, but face challenges like intracellular targets and slow kinetics.[153]

Synaptic loss, a key feature of neurodegeneration, can be imaged via synaptic vesicle glycoprotein 2A, expressed in neurons that release glutamate and γ-aminobutyric-acid, and widely distributed throughout the brain. [^{11}C]UCB-J, and the clinically more applicable fluorinated homologues ([^{18}F]UCB-H, [^{18}F]SynVes-T1, and [^{18}F]SynVes-T2), have shown reduced uptake in regions expected to be affected by neurodegeneration in Alzheimer's disease.[154,155] Synaptic vesicle glycoprotein 2A ligand superiority to validated biomarkers of neurodegeneration like [^{18}F]fluorodeoxyglucose-PET, [^{123}I]-ioflupane single-photon-emission CT, and atrophy on MRI, need further clarification. A CSF synaptic biomarker (ratio of YWHAG to NPTX2 protein concentrations) is under development to predict cognitive decline in Alzheimer's disease, and could help to identify candidates for monoclonal antibody treatment initiation, and might be translated into a blood test.[156]

Innovative biomarkers: digital

Captured via passive (eg, smart watches) or active (eg, cognitive tests) devices, digital biomarkers enable continuous, scalable data collection in real-world settings, and open the door for large-scale risk profiling.[157] Speech features,[158] mobile device use patterns (eg, keyboard typing speed), motor activity, pupillary responses, and personal physiological data have mild cognitive impairment detection rates of up to 85%.[159] The huge amount of collected data requires machine learning and artificial intelligence for analysis.[160]

Substantiating the analytical validity of digital biomarkers will need to be followed by clinical validity (diagnostic accuracy and sensitivity to the early stages) and clinical utility (improved health outcomes).[161] Legal (eg, sharing data with commercial entities), ethical

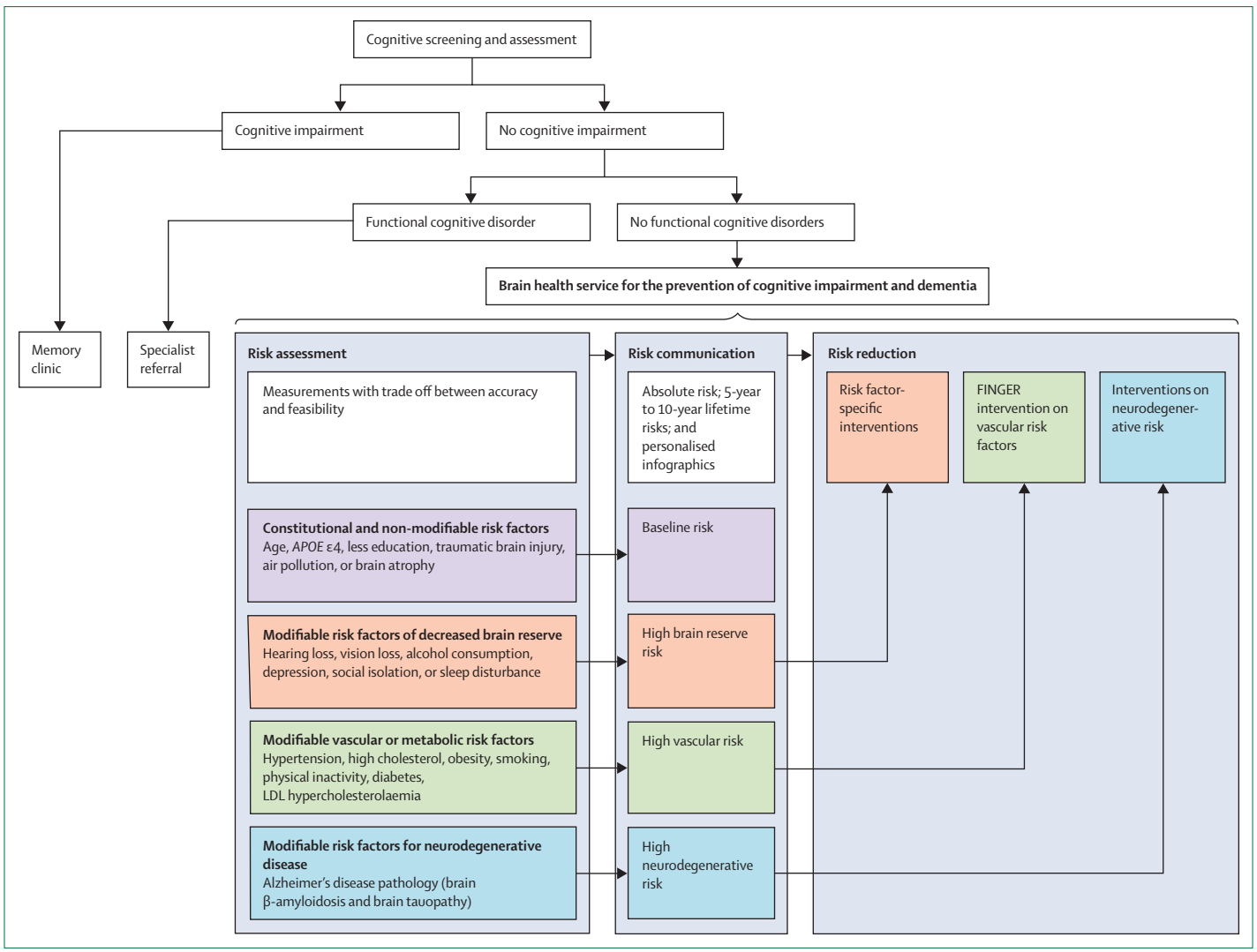

Figure 2: **Patient journey for the secondary prevention of cognitive impairment and dementia in individuals without cognitive impairment who are at risk and are under testing in ad-hoc brain health services**

The cognitive impairment branch is addressed in the first and second papers of this Series.[1,2] The functional cognitive disorder branch requires appropriate specialist referral. FINGER=Geriatric Intervention Study to Prevent Cognitive Impairment and Disability.[167]

(eg, possible biases in artificial intelligence-assisted analysis), and data protection issues (eg, safeguarding sensitive health data from malicious parties) remain necessary for clinical implementation and accessibility.[162,163]

Pharmacological treatments under development

In 2024, there were 182 randomised clinical trials for Alzheimer's disease:[164] 30% testing disease-modifying biologics, 43% disease-modifying small molecules, 14% cognitive enhancers, and 11% neuropsychiatric drugs. Only 33% of investigational products targeted β-amyloid and tau; all others targeted different mechanisms like the gut–brain axis, vasculature, epigenetics, circadian rhythm, growth factors and hormones, *APOE* status, lipid metabolism, neurogenesis, oxidative stress, protein metabolism, bioenergetics, synaptic plasticity, neurotransmitter receptors, inflammation, and immunity.[164] One trial combines anti-β amyloid and anti-tau monoclonal antibodies (NCT05269394). This variety reflects a shift from a deterministic view of the amyloid cascade hypothesis toward more complex and explanatory pathophysiological models accommodating co-pathology and resilience.[165,166]

Targeting cognitively unimpaired individuals at risk of Alzheimer's disease

Memory clinics address patients with cognitive impairment (figure 2).[1,2] However, 13–37% of patients have complaints or worries about declining cognition without objective cognitive impairment (see the first paper of this Series).[1] Currently, clinics have limited

strategies for this expanding group. The European Task Force for Brain Health Services for the secondary prevention of cognitive impairment and dementias (dBHS)[117,168] developed a patient journey involving exclusion of functional cognitive disorders followed by risk assessment, risk communication, personalised risk reduction, and cognitive enhancement (figure 2).[168,169]

Risk assessment evaluates four clinically meaningful categories of risk factors: non-modifiable, modifiable of decreased brain reserve, modifiable vascular or metabolic, and modifiable for neurodegenerative disease (figure 2). Although interactions among pathways are poorly understood, this categorisation helps to compute the pertinent associated risks and direct patients to specific risk-reduction interventions.

Risk assessment balances accuracy and feasibility (eg, pure tone audiometry *vs* whispered voice test).[170] Constitutional and non-modifiable risk factors include the ε4 allele of *APOE*, a strong risk factor for sporadic late-onset Alzheimer's disease, and closely associated with brain β-amyloidosis.[165] Modifiable risk factors of decreased brain reserve affect the capacity of the brain to compensate for biological damage by, for example, activating alternative networks, biochemical pathways, or cognitive strategies.[165]

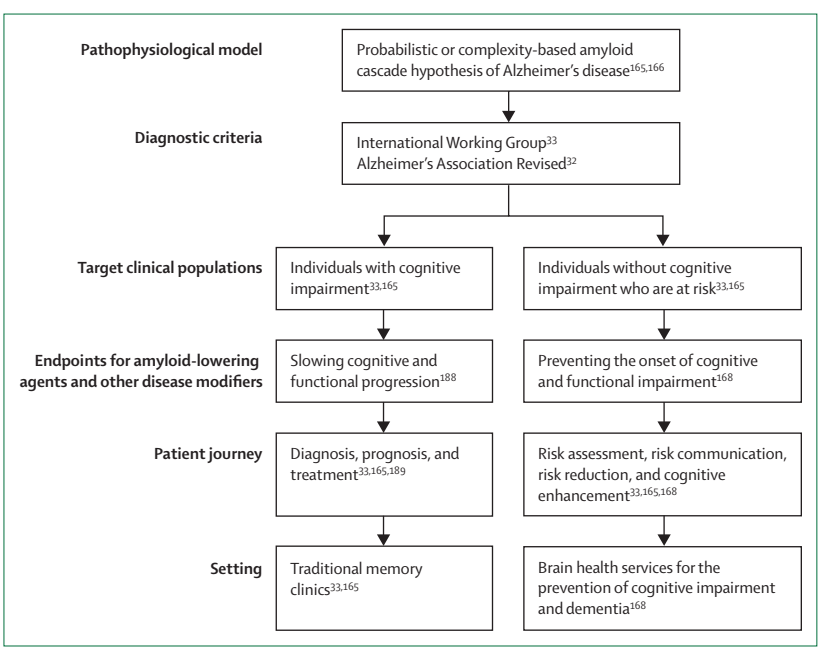

Figure 3: **Diagnostic criteria and clinical pathways**
A coherent scientific and clinical narrative is taking shape in Alzheimer's disease research. Modified versions of the amyloid cascade hypothesis leverage notions of probability or complexity and more satisfactorily account for observed clinical and biological variability.[165,166] Although with different emphasis on the constructs of risk condition and disease, the International Working Group 2024 and Alzheimer's Association 2024 diagnostic criteria[33,34] translate these pathophysiological notions into practice. These diagnostic criteria use amyloid cascade biomarkers to diagnose Alzheimer's disease in individuals with cognitive impairment and identify individuals without cognitive impairment who are at risk of cognitive impairment and dementia.[34] Endpoints are different when testing disease modifiers in individuals with and without cognitive impairment. Specific patient journeys for the two clinical groups are available or are being developed for clinical care.[168] These are being, or will be, delivered in ad-hoc settings.[117,168] Reproduced from Frisoni,[190] with permission from BMJ Publishing Group.

Modifiable risk factors of vascular or metabolic health[171] include risk factors for cerebral microvascular disease and[168] of neurodegenerative diseases include biomarkers of Alzheimer's disease pathology (in particular, scalable blood biomarkers such as p-tau217)[172] as per the diagnostic International Working Group framework.[34,168] More accurate risk estimates are needed in representative cohorts, taking into account the correction for co-occurring risk factors and key risk modifiers such as age.[168,173]

Risk communication should explicitly address the difference between having a disease and being at risk of a disease, use personalised infographics to convey absolute risk over specific timeframes (eg, 5-year risk, 10-year risk, and lifetime risk),[168] and discuss uncertainties associated with translating group-level data to an individual.[174] More data are needed on negative psychological responses to risk disclosure and their management.[117]

Risk reduction aims to mitigate the cumulative damage resulting from vascular and neurodegenerative pathways, modulated by a constitutional and non-modifiable risk background, and by modifiable brain reserve. The multidomain Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) protocol on vascular and metabolic risk factors improves cognitive function in older (60–77 years) individuals at risk.[167] The effectiveness of FINGER-like interventions has been shown in a recent US-based controlled trial[175] and can be effectively delivered via online coaching apps.[176] Risk-reduction interventions on neurodegenerative pathways like anti-β amyloid and anti-tau monoclonal antibodies are in early stages. Drugs targeting senescence (eg, metformin) are also under investigation.[177] Cognitive enhancement via cognitive training and non-invasive brain stimulation can improve attention, executive functions, and memory within weeks, but their effect on long-term cognitive risk is unknown.[178,179]

Several European sites (including Aberdeen, Scotland; Amsterdam, Netherlands; Barcelona, Spain; Cologne, Germany; Geneva, Switzerland; Monza, Italy; Paris, France; and Stockholm, Sweden) are implementing the dBHS model and testing the feasibility, efficacy, and effectiveness of interventions.[117] If proven effective, dBHS will need integration into an ethically and equitably organised prevention network involving primary care, memory clinics, and community services.[180]

Primary prevention

Secondary prevention strategies target individuals at high risk of Alzheimer's disease, but most cases actually arise from low-risk groups strata of the population—the so-called prevention paradox.[181] Estimates suggest that up to 70–80% of cases of dementia arise from normal-risk groups.[182] Measures of Alzheimer's disease neuropathology, such as plasma p-tau217, have not been studied in these risk models, and the contribution of

Alzheimer's disease neuropathology to dementia risk in the population should be elucidated.

Therapies aiming at primary prevention seek to disrupt Alzheimer's disease initiation and prevent pathology onset. Such trials are challenging because participants are typically asymptomatic and Alzheimer's disease-biomarker negative. Long-term studies with interim biomarker outcomes are necessary due to the prolonged preclinical phase of Alzheimer's disease. The DIAN-TU primary prevention trial with remternetug (a subcutaneously administered anti-β amyloid monoclonal antibody) in individuals with autosomal dominant Alzheimer's disease without established β-amyloid plaque pathology, is the first primary prevention pharmacological trial for Alzheimer's disease (NCT06647498). Other strategies include gamma-secretase modulators that increase the efficacy of the enzyme such that shorter, and less aggregation prone, variants of β-amyloid are formed, and genetic therapies targeting underlying genetic drivers like *APOE* ε*4*.[183,184]

Effective primary prevention also involves actions addressing the environments in which individuals live, work, and grow old—ie, the social determinants of dementia.[52] These approaches can benefit large segments of the population without extensive resource mobilisation or individual behavioural changes, implying favourable cost-effectiveness and increased health equity.[35,181,185] 26 population-level interventions and policies have the potential to reduce modifiable dementia risk factors,[186] including fiscal policies (eg, taxing tobacco, alcohol, and sugary drinks), urban and transportation planning (eg, walkable and cyclable neighbourhoods, and cleaner cooking stoves and fuels), marketing restrictions (eg, of tobacco, alcohol, and highly processed foods), and legislative measures (eg, occupational noise protection and helmet mandates).[186] Modelling suggests these strategies are likely cost-saving.[187]

Conclusions

Until recently, the scientific and clinical narratives of Alzheimer's disease were misaligned. Research and drug development were dominated by the amyloid cascade hypothesis, but clinically, diagnostic patient journeys lacked biomarkers related to this pathophysiological framework, and treatments had no effect on amyloid-driven changes. However, this Series shows that, especially in high-income countries, the scientific and clinical narratives around Alzheimer's disease are gradually becoming more coherent—integrating pathophysiology, diagnosis, treatment, and prevention (figure 3).

Many challenges remain. Consensus on what constitutes Alzheimer's disease needs to be reached, similar to efforts with Parkinson's disease and Huntington's disease.[43,191,192] This will impact how Alzheimer's disease is defined in population-based studies and affect incidence and prevalence estimates, identification of risk factor target pathways for innovative drugs, trial design, case selection, and prevention strategies.[193]

This Series paper might not fully explain why Alzheimer's disease treatments are viewed more sceptically than those for other diseases with similar benefits, risks, and costs. Although speculation about historical stigma and the disconnect between public health and basic research is sensible, a substantial body of biological, clinical, public health, and pharmacoeconomics data now allows communities to address the Alzheimer's conundrum[32] as any other treatable and preventable chronic disease. The honest and lively debate among experts will continue. Advances in biomarkers and pharmacological and non-pharmacological prevention methods will support the shared goal of improving cognitive health and quality of life for individuals and communities.

Contributors

GBF drafted the structure of the paper, was responsible for an early draft of the text, and drafted tables and figures. CRJ was the main contributor to the section on the disease-centred approach; BD to the patient-centred approach; CB and SW to the population-centred approach; GBF, EA, OC, and CG to clinical efficacy of biologics for oncology, multiple sclerosis, and rheumatoid arthritis; TH, OC, and CG to contrasting the efficacy of biologics for Alzheimer's disease and other conditions; TH and EA to the comparative societal burden of Alzheimer's disease and table 3; VG, HZ, OH, and KSF to innovative biomarkers; OH, CB, and SW to primary prevention. GBF was the main contributor to the remaining text. All coauthors did the pertinent literature searches, revised the numerous versions of the manuscript, 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 in the Series once completed and agree that the paper they coauthored appears in this Series.

Declaration of interests

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HZ has served at scientific advisory boards and as a consultant for AbbVie, Acumen, Alector, Alzinova, ALZpath, Amylyx, Annexon, Apellis, Artery Therapeutics, AZTherapies, Cognito Therapeutics, CogRx, Denali, Eisai, Enigma, LabCorp, Merck Sharp & Dohme, Merry Life, Nervgen, Novo Nordisk, Optoceutics, Passage Bio, Pinteon Therapeutics, Prothena, Quanterix, Red Abbey Labs, reMYND, Roche, Samumed, ScandiBio Therapeutics AB, Siemens Healthineers, Triplet Therapeutics, and Wave; has given lectures sponsored by Alzecure, BioArctic, Biogen, Cellectricon, Fujirebio, LabCorp, Lilly, Novo Nordisk, Oy Medix Biochemica AB, Roche, and WebMD; is a co-founder of Brain Biomarker Solutions in Gothenburg AB, which is a part of the University of Gothenburg Ventures Incubator Program, without any products on the market; and is co-chair of the Global Biomarker Standardization Consortium and chair of the International Federation of Clinical Chemistry and Laboratory Medicine Working Group on Biomarkers for Neurodegenerative Diseases. 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