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People get ready! A new generation of Alzheimer's therapies may require new ways to deliver and pay for healthcare

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The development of disease-modifying therapies (DMTs) for Alzheimer's disease (AD) has progressed over the last decade, and the first-ever therapies with potential to slow the progression of disease are approved in the United States. AD DMTs could provide life-changing opportunities for people living with this disease, as well as for their caregivers. They could also ease some of the immense societal and economic burden of dementia. However, AD DMTs also come with major challenges due to the large unmet medical need, high prevalence of AD, new costs related to diagnosis, treatment and monitoring, and uncertainty in the therapies' actual clinical value. This perspective article discusses, from the broad perspective of various health systems and stakeholders, how we can overcome these challenges and improve society's readiness for AD DMTs. We propose that innovative payment models such as performance-based payments, in combination with learning healthcare systems, could be the way forward to enable timely patient access to treatments, improve accuracy of cost-effectiveness evaluations and overcome budgetary barriers. Other important considerations include the need for identification of key drivers of patient value, the relevance of different economic perspectives (i.e. healthcare vs. societal) and ethical questions in terms of treatment eligibility criteria.

Keywords: aducanumab, Alzheimer's disease, cost-effectiveness, disease-modifying therapies, lecanemab, performance-based payment models

Background

The prevalence of Alzheimer's disease (AD) and other types of dementia is rising due to a growing and ageing population. In 2019, it was estimated that 55.2 million people worldwide lived with dementia (Table 1). If the increase continues at the current rate, the prevalence has been predicted to reach 78 million by 2030 and 139 million by 2050 [1]. The rise in prevalence, in combination with the high care needs of patients with dementia, poses a growing public health crisis. The global costs of dementia were estimated to be USD 1.3 trillion in 2019, and a substantial proportion of the costs was attributed to informal care, particularly in low-income countries [2] (Table 1). AD is the leading cause of dementia, with a global prevalence estimated to be 32 million in 2020 [3]. There is no cure for AD; traditional treatments, including cholinesterase inhibitors and memantine, treat symptoms without altering the course of the disease. There remains a significant unmet need for new therapeutic interventions that can

From the Think Tank meeting – Innovative payment models in Alzheimer's disease

Table 1. *Prevalence and cost of dementia in 2019, globally and by income level.*

Income level	Prevalence (millions)	Total societal cost (USD billion)	Cost per person (USD)	Proportion of costs (%)		
				Medical	Social sector	informal care
Low-income	1.4	3.5	2 575	4.6	10.5	84.9
Lower-middle income	8.8	44.3	5 010	10.9	13.2	75.9
Upper-middle-income	23.6	293.2	12 414	18.5	18.7	62.8
High-income	21.4	972.3	45 500	15.8	39.9	44.3
Global	55.2	1 313.4	23 796	16.2	34.2	49.6

Sources: Refs. [1, 2].

reduce disease progression, thereby alleviating the societal burden of AD dementia.

AD is characterized mainly by the loss of memory functions and incremental disability performing everyday tasks, leading to increasing care dependence over time. It may initially present as mild cognitive impairment (MCI) in a prodromal phase with subtle changes in cognitive function, but with little functional impact on daily life [4]. The global number of people with prodromal AD was estimated to be approximately 69 million in 2020, which is more than double compared to AD dementia [3]. The symptoms of AD increase gradually over the course of the disease, from memory loss in the prodromal stage of AD dementia to significant functional and cognitive impairment with potentially lethal consequences in the severe clinical phase [5]. It has become increasingly clear that the symptomatic stages are often preceded by decades of preclinical pathological processes. In particular, the accumulation of beta-amyloid protein (Aβ) plaques followed by hyperphosphorylation and aggregation of tau protein filaments have been identified as important early mechanisms, and potential drivers, of AD pathophysiology [6, 7]. These processes have therefore gained attention as promising targets for the development of early AD diagnostics [8] and disease-modifying therapies (DMTs) that can prevent or slow the progression of AD [9, 10].

This growing understanding of the preclinical molecular mechanisms of AD over recent years has resulted in an escalation in the pharmaceutical development of AD DMTs. In January 2022, there were 119 potential DMTs in clinical studies, representing a 60% increase from 2017 [11, 12]. Of all AD medicines in clinical trials in 2022, 83% were DMTs, of which 18% were in phase 3 [11]. However, overall, the success rate of AD DMTs has been low, and only two compounds have so far received regulatory approval in the United States (US). The two beta-amyloid monoclonal antibodies, aducanumab (Adulhelm) and lecanemab (Leqembi), were approved by the US Food and Drug Administration (FDA) in 2021 and 2023, respectively, both under accelerated pathways based primarily on evidence from short-term trials with surrogate markers of clinical benefit (i.e. the reduction in beta-amyloid plaques as a surrogate for cognitive decline) [13, 14]. For lecanemab, a reduction in cognitive and functional decline over a treatment period of 18 months was subsequently demonstrated [15], resulting in lecanemab receiving traditional approval by the FDA [16]. Recently, reduced clinical progression was also observed in a phase 3 clinical trial of another monoclonal antibody, donanemab [17], for which regulatory approval by the FDA is pending [18].

There is an ongoing discussion on whether the effect sizes observed in the phase 3 trials of aducanumab, lecanemab and donanemab meet criteria for minimal clinically important difference [19–22], particularly in relation to potential side effects related to this class of drugs, such as amyloid-related imaging abnormalities (cerebral microhaemorrhages and/or hemosiderosis, detected via magnetic resonance imaging) [22–24]. Yearly drug costs of more than USD 25,000 per patient in the US also raise questions about value and affordability. Nevertheless, as indicated by modelling studies, even modest reductions in AD progression on the individual level could potentially have considerable societal benefits due to the size of the AD patient population [25].

With two AD DMTs on the market and several in the pipeline, difficult questions will need to be answered regarding how these expensive therapies should be valued, reimbursed and used in the

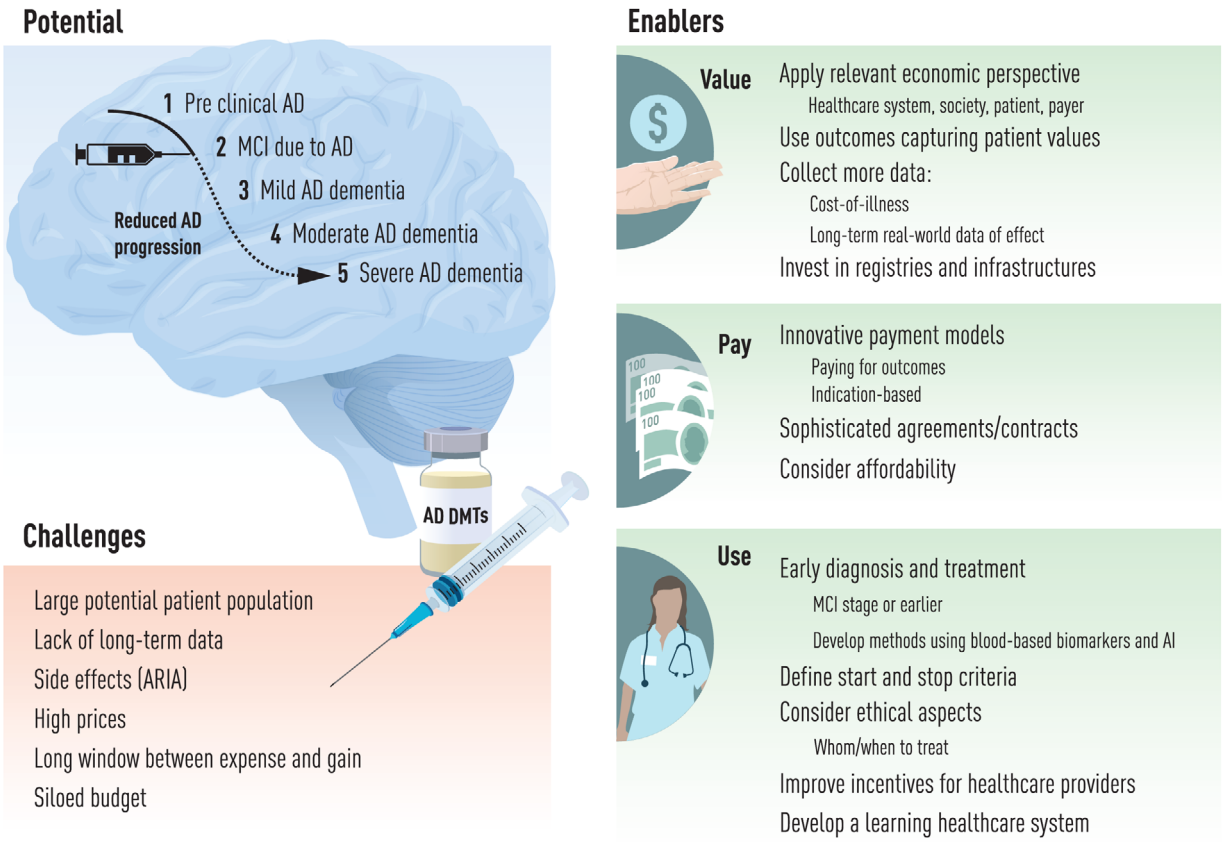

Fig. 1 *Summary of key considerations to prepare for the arrival of Alzheimer's disease (AD) disease-modifying therapies (DMTs). AI, artificial intelligence; ARIA, amyloid-related imaging abnormalities; MCI, mild cognitive impairment.*

healthcare system. Such challenges are not unique to the field of AD, and new pharmaceutical therapies for all diseases should be evaluated in terms of the medical benefits provided in relation to its costs. Pricing and reimbursement of new cancer drugs, for instance, is presenting a major challenge for healthcare systems, whereas advancements in precision medicine may in the future further widen the gap between what is possible and what is affordable. However, the challenge posed by AD is unparalleled due to the high prevalence, the long duration from the earliest symptom to end of life (decades), budget silo effects (who pays and who benefits from treatment), enormous unmet medical need, and the difficulties in determining the value of treatment and aligning the incentives of the multiple stakeholders involved. In this article, we summarize – from the broad perspective of different stakeholders – the most critical measures to ensure health system and payer readiness for the arrival of AD DMTs. A summary of the key considerations is presented in Fig. 1.

How to value the new therapies

New therapies for AD reach the market with limited information on cost-effectiveness and clinical benefit, especially long-term efficacy and safety. Another impediment for accurate cost-effectiveness evaluations is the paucity of comprehensive data on cost-of-illness and health-related quality of life in relation to disease stages in AD, particularly for low-income countries. Filling the knowledge gaps in terms of costs, utilities and mortality associated with AD, accounting for age, is crucial for accurate estimations of potential savings associated with reduced disease progression. However, to capture the full socioeconomic burden of AD, it is necessary to consider and apply a societal perspective that, in addition to direct

medical costs, also incorporates indirect costs associated with caregiver burden and lost productivity [26, 27]. It may also be relevant to include intangible costs associated with reduced quality of life for carers and family [28]. Such 'hidden' costs are likely contributing to a significant proportion of the full real-life costs of AD and may also represent the most highly valued outcomes for patients and caregivers [29].

Moreover, estimating the full cost-effectiveness of reduced disease progression from the patient perspective will require outcomes and endpoints that can provide an objective assessment of key drivers of patient value. Recent studies have reported that outcomes such as independence, identity, emotional well-being and social life – which are not typically evaluated in clinical studies – are highly prioritized among both patients with AD and their carers [28, 30, 31]. Outcomes must also be feasible to collect in real-world settings; seeking advice from clinicians and other staff members close to the patient is therefore crucial.

The lack of long-term treatment efficacy from clinical trials over the full course of disease requires disease and health economic modelling to estimate the long-term cumulative treatment benefits. A major challenge in this context is the unusually long timeframe between treatment start and expected effects; as DMTs are aimed for treatment at the early disease stages when the symptoms are mild, it will be many years until the full impact on clinically meaningful outcomes and patient value drivers can be assessed [27, 32]. However, to delay regulatory approval and market access until data from long-term clinical studies are available would not only restrict access to potentially life-changing treatments for currently eligible patients, but will also increase development costs and lower the incentives of the pharmaceutical industry for AD DMT innovation. A possible solution would be to collect the required long-term data from patients under treatment in a real-world setting (i.e. real-world data [RWD]).

Evidence of the effectiveness, safety and value of AD DMTs under conditions of routine care can be produced through the collection and analysis of RWD. Further, RWD can be used to support innovative payment models (see following section) through which the cost of the therapy is adjusted based on the demonstrated long-term clinical effectiveness.

RWD could be particularly valuable if it captures the full course of the disease. To achieve this, data collection should begin in the early disease stages and continue over the full course of treatment in more specialized settings, including memory clinics. Long-term treatment effectiveness could then be assessed by following treated patients using registries with historical cohort data serving as treatment controls. To facilitate such analyses, more investments in registries are required. There are currently very few registries that prospectively capture patients with AD under routine care conditions. The Swedish Registry for Cognitive Disorders and Dementia (SveDem) [33], established in 2007, has followed over 100,000 patients from diagnosis in specialist or primary care settings with annual visits at which diagnosis, degree of cognitive function, care setting and other key variables are captured [34]. A module for tracking AD DMTs was recently added to the registry. The French National Alzheimer Database (BNA) [35] has included over 500,000 patients with dementia; however, the database includes few patients with early stage AD who may be eligible for AD DMTs [36]. In the US, the Centers for Medicare & Medicaid Services (CMS) has set up a patient registry in which clinicians prescribing AD DMTs are required to submit data at treatment initiation and then every 6 months up to 24 months. Information collected includes diagnosis, concomitant medication, results of biomarker tests, specific antibody being administered, evidence of ARIA and cognitive function [37].

These national initiatives need to be supplemented with international collaboration to set up an infrastructure for follow-up of patients in countries that currently lack registry capabilities. There is also a need to invest in better and universal data infrastructure and the establishment of associated information technology, data and privacy frameworks that allow for the identification of suitable cohorts, harmonization of large-scale data sets and remote access to data.

How to pay for the new therapies

It is certainly plausible that cost-effectiveness can be demonstrated for AD DMTs in comparison with today's standard of care, particularly if a broader societal perspective is appropriately considered during health technology assessment [38–40]. However, it should be noted that the actual spending may differ considerably from estimated societal

costs due to the impact of budgetary restraints. Budget impact and organisational limitations – rather than reasons related to cost-effectiveness – will likely be the main hurdles for getting these new treatments to patients. Another important complication is that budgets across time and institutions are siloed, meaning that those investing in the treatment today (e.g. clinical treatment centres) are not the same as those benefiting from them in the future (e.g. institutional care providers) [41, 42]. This means that a whole system view is required to take into account the full benefits and potential cost savings.

An unsustainable scenario may arise if the currently high price levels for aducanumab and lecanemab are maintained and applied also for future DMTs entering the market. With the high number of potentially eligible patients, the drug expenditures could become extremely high. This could crowd out other and perhaps more cost-effective activities in the healthcare system, affecting all healthcare users [43]. Note that the decision-making frameworks based on cost-effectiveness thresholds are designed for marginal changes, whereas if the budget impact is of a non-marginal magnitude, this may effectively lower the cost-effectiveness threshold. Although budget impact may be ameliorated by efforts to target treatment via tightened eligibility criteria, it would also hamper DMT uptake and fail to address the key uncertainty about long-term value of these treatments in the full patient population that might benefit. Combined with budget impact, uncertainty around long-term outcomes is a critical barrier that needs to be addressed. Slow uptake and constrained access would limit opportunities to collect patient data that can elucidate the long-term value of DMTs, and also disincentivize investment in future AD research and development (R&D), thereby further exacerbating the relatively low spending on R&D in this complex disease area.

A possible solution to manage budgetary constraints, as well as address uncertainty, are innovative payment models that limit the financial risk for the healthcare provider [42, 44, 45]. Such managed entry agreements (MEAs) – also commonly referred to as risk-sharing agreements, or patient access schemes – can be used to improve the efficient use of new technologies and to address uncertainties regarding their performance. MEAs can be divided into financial agreements, which primarily manage uncertainties in terms of budget impact, and performance-based agreements, by which payment is contingent upon the patient outcomes obtained with real-world use of the product. Financial and performance-based agreements can be further divided based on whether the agreements are defined at the patient or population level [46].

For AD DMTs, performance-based payment models may prove particularly advantageous due to the high degree of uncertainty regarding long-term effectiveness. Different types of performance-based models include coverage with evidence development (CED) and pay-for-performance, also referred to as outcome-based payments (Fig. 2). In CED, the payer provides temporary coverage of the treatment, with the decision being revisited at a later date based on an assessment of data collected on the outcomes in practice. In contrast, pay-for-performance models could mean that payers incur treatment costs that are proportional to the treatment benefit (Fig. 2), receive refunds if expected outcomes are not met, or delay payment until expected outcomes are met [46, 47].

Intuitively, applying similar models for AD DMTs could address some of the critical challenges with these therapies, such as the heterogeneity and uncertainty in long-term treatment response (Fig. 2). Such arrangements would allow decision uncertainty to be addressed, while permitting payment only when a medicine works as intended. As well as mitigating the risk for payers and addressing their decision uncertainty, it would also lead to further data collection to strengthen the evidence base for such treatments and allow providers to closely monitor outcomes and manage costs. Most importantly, they could allow patients earlier access to potentially valuable treatments than they might otherwise be granted.

However, the large patient population, long time frames in terms of potential benefit, and cost and burden of data collection will provide challenges. Another major challenge is the need for pre-specified outcomes and endpoints with sufficient sensitivity to demonstrate potential treatment effectiveness, particularly in early AD [42, 48]. It will be necessary to design schemes that balance the need to address uncertainty in long-term outcomes with the practicality of collecting data in a short-enough timeframe to make contracting over these outcomes acceptable for all parties.

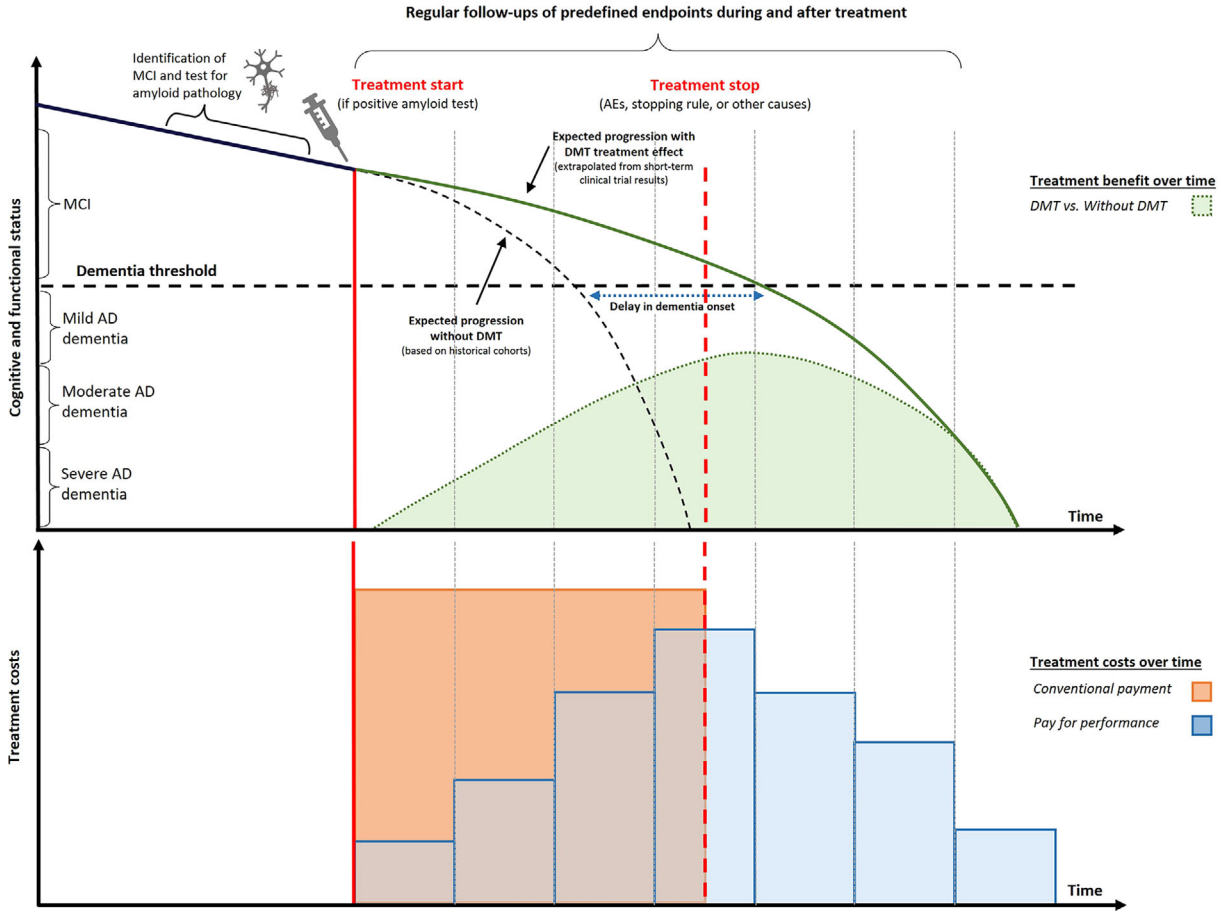

Fig. 2 *Relationship between a hypothetical Alzheimer's disease (AD) disease-modifying therapy (DMT) treatment effect and potential payment models for treatment costs. With conventional payment models, costs are incurred at a constant level while patients remain on treatment (i.e. between treatment start and treatment stop). With the illustrated hypothetical pay-for-performance payment model, costs are incurred at a level proportional to the magnitude of treatment benefit (e.g. relative to historical control) and could continue beyond the duration of treatment. Other outcomes-based payment models (not illustrated) could include refunds for patients not meeting a predetermined outcome at a specified assessment point or delayed payment until a predetermined outcome has been achieved. Although not required, total treatment costs with pay-for-performance models could be set to match those with conventional models. Pay-for-performance models could be defined on an individual patient level or on a cohort level. AE, adverse event; MCI, mild cognitive impairment.*

Previous experiences of performance-based payment schemes from other chronic progressive disease areas are limited and the overall success rate not thoroughly evaluated [28].

Succeeding with innovative payments models for AD DMTs will require trust and willingness among the different parties, as well as elaborate and sophisticated agreements and contracts. The process of developing such agreements should begin at an early stage of drug development. To bring all parties to the table, the shared belief of a win–win situation is important. Issues that should be managed in agreements include information governance (i.e. how and by whom data can be legitimately and legally collected, assessed and used) and how to handle different scenarios such as missing or delayed data. Involving a trusted third party (e.g. an independent arbiter) to oversee contract arrangements, as well as data analysis and execution of the payment or rebate process, is likely to be necessary [49, 50].

How to use the new therapies in healthcare

Initiating treatment with DMTs at early disease stages appears to be a key premise to achieve the best possible outcomes. Modelling of life-time effects of lecanemab has implied that treatment initiated at the MCI stage, or at early tau-pathological stages, could double the gain in quality-adjusted life-years compared to treatment initiated in mild dementia [51]. Timely diagnosis and early identification of patients eligible for treatment will require biomarkers of amyloid pathology. Biomarkers may also be used to predict treatment response and value for the patient when the clinical symptoms of dementia are still mild [4]. Although biomarker confirmation via positron emission tomography (PET) imaging and cerebrospinal fluid (CSF) can detect early amyloid and tau pathology in the brain [52], many patients do not currently receive a biomarker-based confirmatory diagnosis in regular clinical settings, and often diagnoses are received in the later stages of the disease [4]. The proactive risk-based approach to identification of individuals who may go on to develop AD would require the adoption of broader large-scale screening measures and less costly detection and diagnostic tools.

The development of new biomarkers for non-invasive, high-throughput detection of pre-symptomatic AD would greatly improve the diagnostic capacity. Blood-based biomarkers that can be used in regular clinical practise are currently under investigation, but challenges in terms of sensitivity remain, and further validation is required before they can replace PET and CSF biomarkers in standard practise [53, 54]. Moreover, digital biomarkers (e.g. data collected by motion and light sensors) have shown promising potential for detecting cognitive and functional changes associated with early stages of AD [55], and artificial intelligence may provide a powerful tool for early identification of AD signatures from scans, speech data and biomarkers [56]. To support early detection, it will be necessary to allocate the responsibility to primary care instead of specialist care. In many countries, this may require considerable adjustments to the existing primary care system, including scaling up capacities, acquiring new diagnostic tools and training staff.

Another challenge with AD DMTs is the definition of treatment start and stop criteria. DMTs currently entering the market have regulatory approvals for treatment of patients in early symptomatic disease (i.e. prodromal to mild AD) and confirmed amyloid pathology. The total global prevalence of symptomatic AD has been estimated to be approximately 100 million, of which prodromal AD (i.e. MCI stage) represented 68%, and AD dementia 32% [3]. This implies that the population of potentially eligible patients will be considerably larger for DMTs compared with traditional AD therapies indicated for treatment of dementia symptoms. It should also be considered that the number of persons with subjective memory problems who may demand diagnostic work-up will likely be even larger, further adding strain on health system capacities and budgets [57]. Thus, without focusing diagnosis and treatment resources on those with the greatest potential benefits based on strict and rationally based eligibility criteria, the cost of diagnostics and treatment will likely challenge healthcare budgets. This, in turn, could increase the risk of unequal access to treatment in favour of patients with higher socioeconomic status.

The definition of criteria determining whom and when to treat will require careful ethical consideration. Patients in the early and milder disease stages may benefit the most in terms of outcomes; however, limiting treatment eligibility to this group challenges the traditional ethical principles of prioritizing patients with the greatest needs. Moreover, screening and early diagnostics increase the risk of treating 'false positives', which could cause unjustified anxiety, treatment burden and side effects in people who would never progress to clinical AD [58]. In this context, improved primary care capacity for assessments and generation of evidence is needed so that patients are given the opportunity of informed decisions. It is also important that doctors take ethical responsibility in decisions regarding treatment eligibility. Similarly, to avoid unnecessary patient burden in non-responders, consensus stopping rules must be established. For AD DMTs, this is challenged by the current lack of definition around response to treatment and variability in understanding of clinical meaningfulness.

Another important consideration is the potentially low incentives for healthcare providers to introduce early AD diagnosis and DMT treatments due to siloed budgets. Providing large-scale, high-quality diagnosis – thereby identifying more patients

eligible for treatment – could be considered an economic punishment if the payer will not benefit from the economic gain further down the care pathway – for instance, from reduced institutional care. A solution could be a payment reform that provides better longitudinal AD care. As an example, in the US, the current fee-for-service payment system could be changed to a system in which medication is included as part of the total cost of care benchmark.

The new requirements of large-scale screening and early diagnosis, a high volume of patients and potentially long-term treatments with regular monitoring introduced by AD DMTs will put tremendous additional strain on healthcare systems, both in terms of costs and capacity. A lack of healthcare system readiness for AD DMTs has been highlighted in reports from the US and Europe [59], which also emphasized the importance of different stakeholders collaborating to address detection, diagnosis and treatment capacity restraints in a timely manner. Nevertheless, we propose that the challenges associated with the arrival of AD DMTs may provide a unique incentive for systematic healthcare transformations to achieve what has been called a learning health system (LHS) [60]. An LHS is a healthcare system 'in which science, informatics, incentives, and culture are aligned for continuous improvement and innovation, with best practices seamlessly embedded in the delivery process and new knowledge captured as an integral by-product of the delivery experience' [61]. Investing in new diagnosis and treatments for early AD may require disinvestment in older, less effective treatments. In an LHS, evidence is systematically gathered and shared with clinicians to improve decision-making, which will create a mechanism to lower the risk of continued use of treatments that are not cost-effective [60].

Summary and recommendations

This article has reviewed current challenges with the introduction of DMTs for AD in routine clinical practice. Many of these challenges stem from (1) uncertainty about their long-term clinical and economic effects, making it difficult to determine the cost-effectiveness of these treatments; and (2) the mismatch between high up-front costs of earlier detection, biomarker-based confirmatory diagnosis, treatment and monitoring, and the related value which will largely occur years later and accrue to different stakeholders. The high prevalence, the significant unmet need and the progressive nature of AD bring to bear challenges on a unique scale and complexity, and which demand urgent solutions.

This gives reason to believe that conventional payment mechanisms are unlikely to provide a satisfactory solution. New alternative payment models will likely be needed due to the large variability between healthcare systems; however, there are a few common prerequisites for enabling new payment models based on real-world outcomes. First, establishing systems for follow-up and data collection in routine care is a critically important capability to develop. This should ideally be in place before the introduction of new therapies to establish a representative control population against which to evaluate new interventions. Currently, there are only a few dementia registries in Europe (e.g. in Sweden [33] and France [35]) which follow patients longitudinally. Second, stakeholders must come to an agreement on the appropriate outcomes on which to assess real-world treatment effectiveness. Much has already been written on measuring outcomes in routine care [62]. In practice, the actual choice of potential outcome measures is limited, as these will have to be based on data that can readily be collected at scale in diverse care settings. Finally, as the care for patients with AD is organised differently between healthcare systems but often involves multiple care providers and sources of funding, it will be important that a dialogue is initiated in each country between the relevant stakeholders to identify the need for alternative payment models and how these could be adapted to local conditions. Having such discussions well before decisions on the pricing and reimbursement of new therapies could make progress more likely.

Author contributions

Conceptualization; investigation; writing – original draft, writing – review and editing: Karin Wahlberg, Bengt Winblad, Amanda Cole, William L. Herring, Joakim Ramsberg, Ilona Torontali, Pieter-Jelle Visser, Anders Wimo, Lieve Wollaert and Linus Jönsson.

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Conflict of interest statement

William L. Herring is an employee of RTI Health Solutions, a business unit of RTI International. He provides research consulting services for pharmaceutical companies as part of his employment with RTI Health Solutions; Amanda Cole is employed by the Office of Health Economics, which carries out research and consulting for a broad range of funders, including pharmaceutical companies; Ilona Torontali is an employee of and stockholder in F. Hoffmann-La Roche. No conflicts of interest have had any bearing on the content of the current manuscript.

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