KPMG

Alzheimer's in the UK

An opportunity to innovate

Summary

Dementia is one of the most pressing public health issues for the global ageing population, for which there is no known cure. In the UK, over 900,000 people were living with dementia (PWD) in 2021, with a corresponding economic impact of £25bn, and by 2050 this figure is expected to rise to 1.6 million PWD. These figures should provide sufficient incentive for policymakers and clinicians to identify dementia earlier and embrace the impending influx of novel disease-modifying therapies (DMTs).

2021 saw the first new approval in 20 years for Alzheimer's Disease (AD), the most common form of dementia, with Biogen's amyloid-targeting antibody aducanumab (ADUHELM). Although this product was marred with controversy over its clinical data and ultimately withdrawn from global commercialisation, Eisai's follow-up lecanemab (LEQUEMBI) was granted FDA accelerated approval in 2023 following definitive clinical efficacy. The launch of these products has led to a flurry of R&D activity, with even more DMTs (and even curative approaches) on the horizon.

The lead-up to DMT launch gives the UK an opportunity to transition the AD clinical pathway from a largely reactive process focusing on symptomatic management, to a proactive process that prioritises early identification for maximum therapeutic (and downstream economic) benefit.

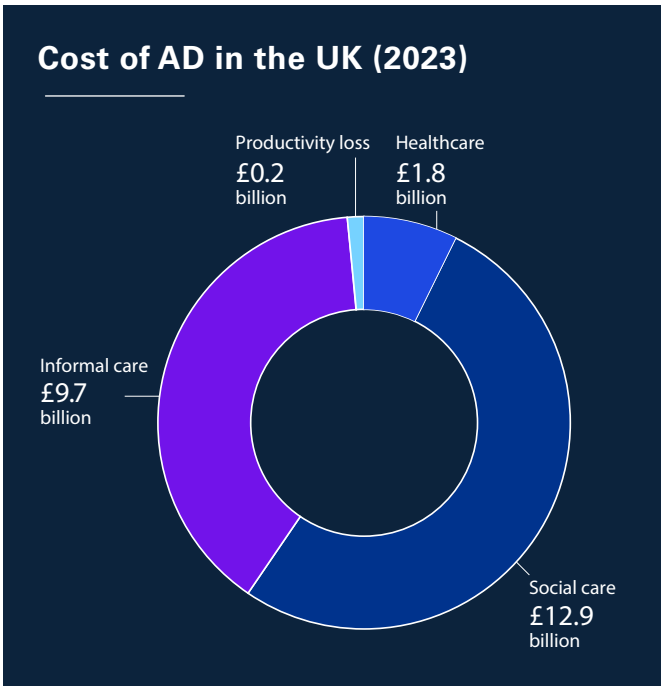
1. Prevalence and Incidence, Dementia Statistics Hub, Alzheimer's Research UK, 2023
2. The Impact of Dementia, Dementia Statistics Hub, Alzheimer's Research UK, 2023

The case for developing the AD care pathway

AD is estimated to be the UK's costliest health condition by 2030

In 2021, the estimated cost of AD dementia in the UK was £25 billion and this is expected to balloon to £47 billion by 205. This comprises both direct health and social care costs (i.e., to the NHS and costs of custodial care) and indirect economic costs (i.e., unpaid family member care and lost employment productivity). Despite the ~1.1 billion hours spent each year on unpaid care for PWD, the largest contributor overall are social care costs, which are expected to triple over the next two decades to £45 billion.

Investment in early diagnosis and intervention may incur greater upfront costs but these will likely result in substantial future savings for the healthcare system through reduction in care needs and institutionalisation. A cost-benefit analysis of such investment should consider a range of economic endpoints including more time spent at work, less time spent in care homes, hospital bed days, emergency admissions, state funded care.



1. The Impact of Dementia, Dementia Statistics Hub, Alzheimer's Research UK, 2023
2. What are the costs of dementia care in the UK? Alzheimer's Society, 2023
3. Alzheimer's Disease – Why we need early diagnosis, 2019, Degenerative Neurological and Neuromuscular Disease, Pages 123-130
4. Reducing the Impact of Dementia in America: A Decadal Survey of the Behavioral and Social Sciences, 2021, National Academies Press (US)
5. The economic value of dementia research, Alzheimer's Research UK, 2023

Healthcare perspectives in AD care

What needs to change with the advent of DMTs?

Patient Identification – the importance of reducing stigma and early detection

Challenges in patient identification arise from both a patient's and a health care professional's (HCP) perspective. The stigma associated with an AD diagnosis can hinder patients from self-referring and seeking care, especially for minority groups facing widened care gaps. Additionally, lacking symptom awareness, particularly in the early stages of AD, when symptoms are undifferentiated, may further delay self-referral. As well as the devastating psychological impact of an AD diagnosis, there are other quotidian effects including the legal obligation to declare a diagnosis to the DVLA and the impact on insurance premiums or employment.

For early diagnosis to be plausible, it's essential that individuals do not feel they are being 'penalised'.

For HCPs, arriving at an AD diagnosis can be challenging particularly in the earliest stages of the disease when cognitive impairments can be minor or not specific to AD. In addition, many recommended clinical rating scales (e.g., ADAS, MoCA, CDR-SB) have a degree of subjectivity and cannot adequately subtype dementia. For some HCPs, further hesitancy to establish or disclose a diagnosis is caused by a perceived dearth of local services to support PWD post-diagnosis and unclear or prolonged referral pathways. HCPs may also see AD as a disease of futility owing to its progressive nature, and therefore reluctant to disclose a diagnosis.

Abbreviations: ADAS – Alzheimer's Disease Assessment Scale; MoCA – Montreal Cognitive Assessment Test; CDR-SB – Clinical Dementia Rating Scale Sum of Boxes

In 2021, it was revealed that average waiting time from GP referral to dementia diagnosis is 17.7 weeks. This is problematic in the context of DMT use as patients risk "out-progressing" their eligibility simply waiting to see a specialist.

CASE STUDY

Can dementia diagnosis be incentivised?

In 2014/2015 NHS England launched a Dementia Identification Scheme, paying GP practices £55 per additional patient diagnosed with dementia. The Scheme was designed to reward GP practices for undertaking a proactive approach to identify patients with dementia. GPs are able to make a diagnosis and will not necessarily refer cases to secondary care services. The scheme was short lived, and was not extended post March 2015, reason being that it was ethically questionable and damaging to relationships between doctor and patient, as decisions about individual's care should be based on clinical need rather than financial imperatives. When announcing the incentive will stop it was described as a one-off activity for practices to catch up if they wished.

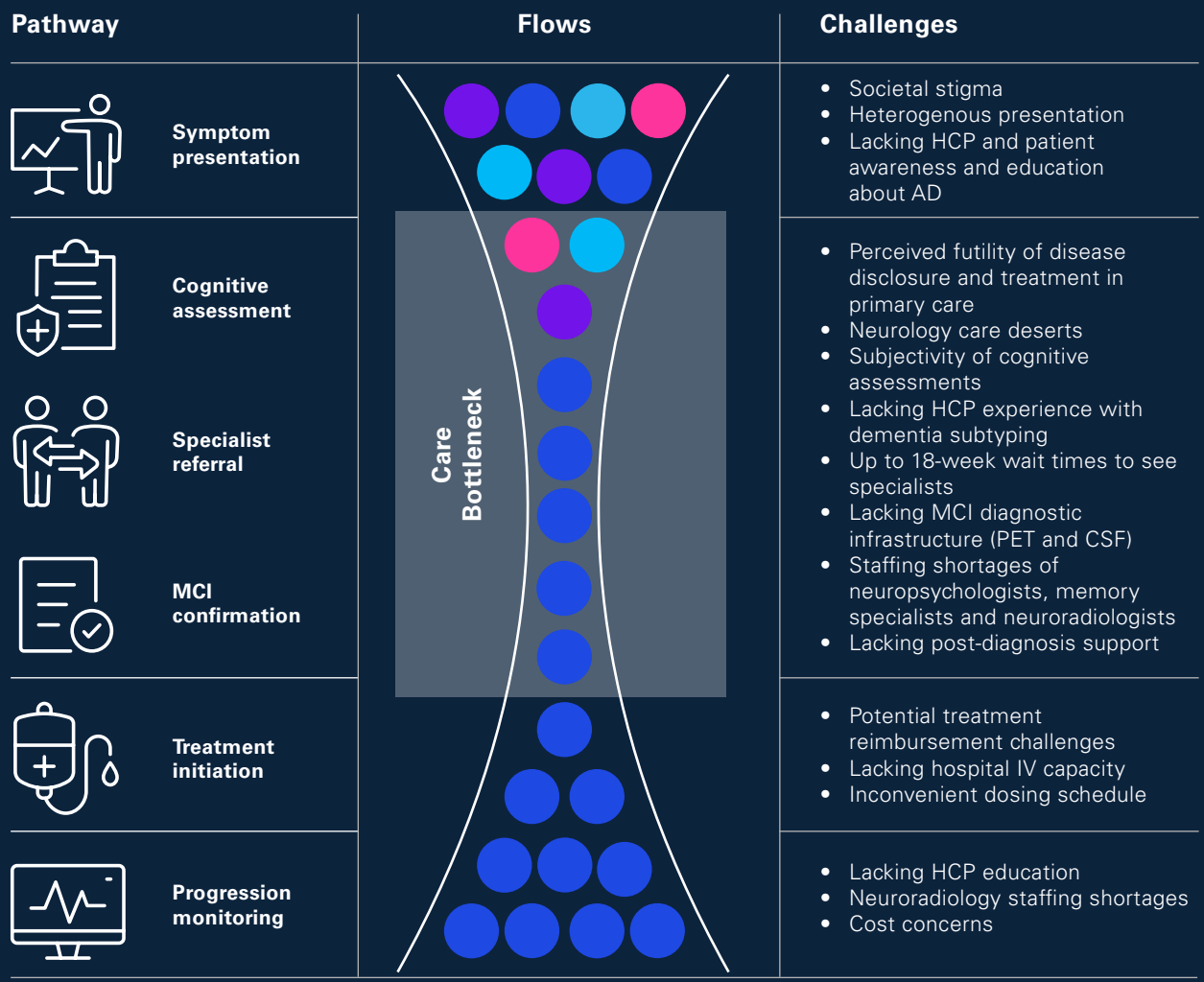
Whilst this scheme was flawed, and subsequently discontinued, the scheme had a positive impact on the national diagnosis rate. Pro-active identification should continue to be encouraged, but future initiatives would need to consider the potential consequences on relationships, as mentioned above, and on workload.

1. Facilitators and Barriers to Dementia Assessment and Diagnosis: Perspectives From Dementia Experts Within a Global Health Context, 2022
2. Alzheimer's Disease – Why We Need Early Diagnosis, 2019
3. Patient-specific cognitive profiles in the detection of dementia subtypes, Alzheimer's Association
4. People with dementia face up to a two year wait for diagnosis, Alzheimer's Society
5. Enhanced Service Specification, Dementia Identification Scheme, NHS England
6. Doctors condemn "unethical" £55 payment for every new dementia diagnosis, theBMJ
7. Increasing access to a dementia diagnosis, Alzheimer's Society

MCI Confirmation – the largest bottleneck in the AD care pathway today

The key bottleneck in the pathway to access DMTs will be obtaining confirmed diagnosis of mild cognitive impairment (MCI). Clinically, this is characterised by problems affecting memory, problem solving, thinking, attention, concentration, language and/or visual ability. To access a DMT, MCI should be confirmed with a clinical assessment (e.g.,10-point cognitive screener) and a physiological test confirming amyloid pathology. While there are challenges to using AD clinical assessments (including user subjectivity and cultural bias), it is expected that care pathways will need to shift to accommodate proactive (MCI) AD testing. Physiologically, the "gold standard" method for AD testing is the quantification of amyloid plaques through positron emission tomography (PET). However, there are significant barriers to PET owing to its cost (up to £3,000 per scan charged to payers) and availability (the UK only has 78 PET scanners, most of which are allocated to oncology testing), necessitating the development of more economic and scalable methods.

Bottlenecks in the AD clinical care pathway



Fortunately, alternatives to PET do exist that can facilitate DMT access. In the immediate-term, measurement of amyloid species in cerebrospinal fluid (CSF) has been recommended by NICE since 2018. A growing body of evidence also shows that amyloid and tau can be detected in plasma and even predict AD progression years before symptom manifestation. The first test, PrecivityAD®, measuring plasma amyloid, was granted FDA breakthrough device designation in 2019, with other major diagnostics players such as Roche and Quanterix developing rapidly scalable diagnostic methods that can expedite treatment access.

Since cognitive assessments have long sufficed as the sole diagnostic method, dementia subtyping will be a relatively new concept to many HCPs outside of a research setting. The increased availability of AD testing will therefore need to be supplemented with adequate education on how dementia subtyping can lead to changes in management, namely treatment with DMTs.

Other Considerations – managing and monitoring patients

Since most of the anti-amyloid DMTs will be administered via IV infusion at least initially, adequate capacity will need to be established. In the US, where DMTs have already launched, short-term "fixes" included repurposing capacity from other departments (e.g., oncology or research capacity). Considerations should also be made towards patient transportation to infusion facilities.

A particularity with amyloid-targeting therapies is the risk of amyloid-related imaging abnormalities (ARIA). These manifestations, detectable through MRI, may indicate brain swelling or small bleeds seen in ~25% of clinical trial patients. ARIA monitoring is recommended, with the frequency left to physician discretion. In the UK, key implementation considerations include scanning costs, neuroradiologist experience, and staffing or scanner capacity.

1. Symptoms of dementia, NHS
2. Dementia: assessment, management and support for people living with dementia and their carers, NICE
3. Accuracy of the Clinical Diagnosis of Alzheimer Disease at National Institute on Aging Alzheimer Disease Centers, 2005–2010, Journal of Neuropathology & Experimental Neurology, Volume 71, Issue 4, April 2012, Pages 266–273
4. Brain amyloid pet scans enhance the diagnosis of Alzheimer's, Alzheimer's Research UK
5. There is still much to do to defeat Britain's biggest cancer killer, HSJ
6. C2N Diagnostics Receives Breakthrough Device Designation from U.S. FDA for Blood Test to Screen for Alzheimer's Disease Risk
7. Roche's Elecsys Amyloid Plasma Panel Granted FDA Breakthrough Device Designation to Enable a Timely Diagnosis of Alzheimer's Disease Press Release
8. Quanterix Links Up With Eli Lilly For Alzheimer's Blood Biomarker Testing Collaboration Press Release
9. LEQUEMBI Prescribing Information, FDA
10. Two Randomized Phase 3 Studies of Aducanumab in Early Alzheimer's Disease, The Journal of Prevention of Alzheimer's Disease, Volume 9, March 2022, Pages 197-210
11. Lecanemab in Early Alzheimer's Disease, New England Journal of Medicine, Volume 388, January 2023, Pages 9-21

Life Sciences Perspectives

What advances are coming down the line and how can they be implemented into clinical practice?

The AD treatment landscape is evolving rapidly

In 2021, Biogen claimed ADUHELM's approval as "the first new AD treatment in nearly 20 years" (indeed the last AD approval was memantine in 2003). Prior to ADUHELM, AD treatment was limited to symptomatic management (e.g., acetylcholinesterase inhibitors like donepezil [ARICEPT]).Following ADUHELM's withdrawal from global commercialisation in early 2024, LEQUEMBI is the most commercially advanced DMT in the US (and also under review in the EU/UK). A third anti-amyloid, donanemab, is expected to launch in 2024.

The renewed interest in AD therapeutics is in stark contrast to the last 10-15 years, which saw Pharma withdraw from neurology altogether. A better understanding of pathophysiology and pharmacological advancements (i.e., crossing the blood-brain barrier) underpin the industry's renewed in interest and risk appetite towards AD therapeutics today. In fact, >130 unique candidates are now in development. These include disease-modifying small molecules, antibodies, and RNA therapeutics, and even potentially curative cell and gene therapies and therapeutic vaccines.

Whilst treating AD in the MCI stage is an advance in itself, preventative approaches may be even more effective. To this end, LEQUEMBI (AHEAD 3-45, NCT04468659), and donanemab (TRAILBLAZER-ALZ 3, NCT05026866) are undergoing trials in preclinical AD. These trials will inevitably be longer than their MCI counterparts owing to the requirement for large cohorts and multi-year follow-up. For example, AHEAD 3-45 participants will be treated for 216 weeks versus 78 weeks in the CLARITY AD MCI study. Nonetheless, as DMT use becomes more mainstream and dementia is destigmatised, a prophylactic approach to AD care could be in reach.

The AD technological landscape is also developing at pace with therapeutics

The advent of novel AD therapies has led to a boom in diagnostics and clinical decision-making tools. Blood-based biomarkers purport to diagnose and stage AD en masse, while digital tools aim to improve and promote earlier AD screening. By leveraging AI, these tools can assess cognition through changes in speech, retinal movements, or gameplay performance. Digital assessments offered in different languages also improve accessibility for marginalised/minority populations (e.g., Cognetivity's ICA). Overall, these innovations will play a role in increasing patient awareness, reducing clinician burden, and driving precision medicine approaches to treatment.

1. Biogen and Eisai launch multiple initiatives to help patients with Alzheimer's disease access ADUHELM™, Biogen
2. NAMENDA (memantine) Drug Approval Package, FDA
3. Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease, NICE
4. Biogen to Realign Resources for Alzheimer's Disease Franchise, Biogen
5. FDA Grants Traditional Approval for LEQEMBI® (lecanemab-irmb) for the Treatment of Alzheimer's Disease, Eisai
6. Lilly's Donanemab Significantly Slowed Cognitive and Functional Decline in Phase 3 Study of Early Alzheimer's Disease, Lilly
7. BMS exits hep C, diabetes and neuroscience drug discovery, PM Live
8. Pfizer exits neuroscience, Nature News in Brief
9. Clinicaltrials.gov extract updated to January 2024

Estimated launch timelines of anti-amyloid antibody therapies

Name	Company	Trial readout	Launch[i] (est.)	Route of Administration
Aducanumab (ADUHELM)	Biogen & Eisai	ENGAGE and EMERGE (Aug 2019)	Withdrawn (2024)	Q4W IV
Lecanemab (LEQUEMBI)	Eisai & Biogen	CLARITY AD (Dec 2022)	US (Jan 2023) UK (2024 est.) EU (2024 est.)	Q2W IV QW SC
Donanemab	Lilly	TRAILBLAZER-ALZ 2 (Apr 2023)	US (2024 est.) UK (2025 est.) EU (2025 est.)	Q4W IV

Navigating the pipeline: AD clinical trials at a glance

AD Tx in development

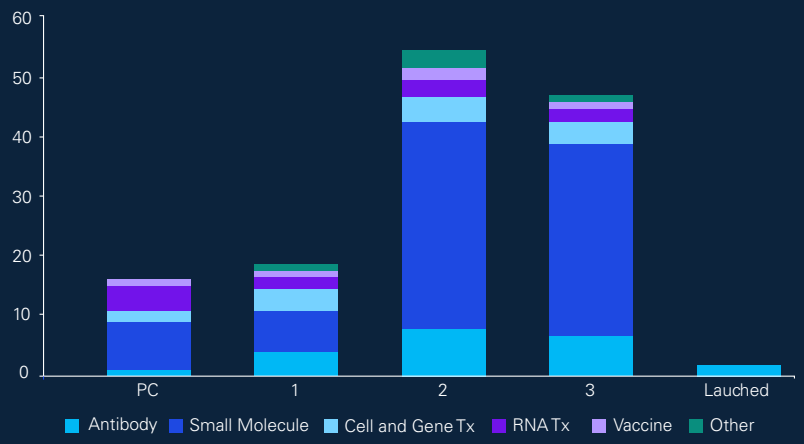


Figure Sources:
Clinicaltrials.gov extract updated to January 2024

1. EMERGE and ENGAGE Topline Results: Two Phase 3 Studies to Evaluate Aducanumab in Patients With Early Alzheimer's Disease, Biogen
2. Biogen to Realign Resources for Alzheimer's Disease Franchise, Biogen
3. Lecanemab Confirmatory Phase 3 Clarity AD Study Met Primary Endpoint, Showing Highly Statistically Significant Reduction of Clinical Decline In Large Global Clinical Study Of 1,795 Participants With Early Alzheimer's Disease, Eisai
4. FDA Approves LEQEMBI™ (lecanemab-irmb) Under the Accelerated Approval Pathway for the Treatment of Alzheimer's Disease, Eisai
5. Marketing Authorization Application for lecanemab as treatment for early Alzheimer's disease accepted by European Medicines Agency, Eisai
6. Eisai Presents New LEQEMBI® (lecanemab-irmb) Investigational Subcutaneous Formulation Interim Study Results and Clinical Improvement Data in Earlier Stages of Early Alzheimer's Disease From Additional Analyses of Clarity AD at The Clinical Trials on Alzheimer's Disease (CTAD), Eisai
7. Lilly's Donanemab Significantly Slowed Cognitive and Functional Decline in Phase 3 Study of Early Alzheimer's Disease, Lilly
8. Why Eli Lilly Stock Could Start Off 2024 With a Bang, NASDAQ

Abbreviations: IV – intravenous infusion; SC – subcutaneous injection

Notes: (i) FDA Accelerated approval authorisation dates or estimates provided

Pharma's role in developing care pathways

Given the plethora of clinical and economic challenges in the evolving AD care pathway, Pharma companies have a role to play in the "change management" required for earlier AD detection and wider use of DMTs.

CASE STUDY

Example activities conducted by Pharma to develop the AD care pathway:

Is there an opportunity for Pharma to partner with PAGs to redefine the AD care pathway?

Within AD, Patient Advocacy Groups (PAGs) are a key stakeholder with a strong voice in the UK and globally. They have not only been influential in campaigning for the approval of new AD treatments, but also in advocating for greater access to timely and accurate diagnostic technologies. Consequently, PAGs are actively seeking to collaborate with Pharma to deliver greater benefits to PWD, through co-funding projects and providing or receiving advice. When considering pathway development initiatives in the UK, Pharma stakeholders should consider the value of the patient perspective through PAG engagement.

Patient pathway step	Activities conducted by Pharma	Examples
Symptom Presentation	• Destigmatise AD and memory pathology • Increase awareness and access to early screening tools • Encourage proactivity in seeking treatment for memory issues	Biogen and CVS collaborated to launch a programme promoting 'brain health', and making screenings available for minority and underserved communities
Cognitive Assessment	• Promote adherence to clinical guidelines • Advance diagnostic technologies • Improve access to advanced diagnostic tests	Eisai launched a research collaboration with Gates Foundation, Life Arc, the University of Edinburgh, and Health Data Research UK to create new digital diagnostic tools for dementia
MCI Confirmation	• Further the development of blood-based biomarkers • Enable access to other confirmatory testing • Support clinicians to navigate their local diagnostics infrastructure • Bridge gaps in the diagnostic pathway	Lilly has partnered with four NHS trusts to increase the capability and capacity for CSF AD testing by junior doctors and advanced nurse practitioners
Treatment Initiation	• Help addressing capacity constraints through patient support services (mobile administration clinics, nurse training, patient transport)	Eisai's "Temporary Support Program" allows free supply of lecanemab for up to 75 days whilst eligible patients await coverage determination
Progression Monitoring	• Collaborate with key opinion leaders (KOLs) to develop of robust clinical guidelines • Educate radiologists to interpret ARIA scans	Biogen provided dedicated educational sessions and instructional resources for clinicians and radiologists around ARIA

Extrapolating some of these tactics and others into the NHS may serve to rapidly advance the UK's AD diagnostic and therapeutic infrastructure, leading to enhanced patient experience and improved clinical and economic outcomes.

1. A remote speech-based AI system to screen for early Alzheimer's disease via smartphones, Alzheimer's & Dementia : Diagnosis, Assessment & Disease Monitoring, Volume 14, Issue 1, November 2022, Page e12366
2. A deep learning model for detection of Alzheimer's disease based on retinal photographs: a retrospective, multicentre case-control study, The Lancet, Volume 4, Issue 11, September 2022, Pages E806-E815
3. AIRAmed Receives FDA 510(k) Clearance for Its AIRAscore Brain Volumetry Software, AIRAmed
4. Connectivity Neurosciences Website
5. Biogen unveils collaborations with CVS Health, Cigna to boost access to its Alzheimer's drug, Fierce Healthcare
6. Eisai launches Gates-backed research collab to develop digital tools for dementia diagnosis, treatment, Fierce Biotech
7. Nurses 'central' to new plans to improve Alzheimer's diagnosis, Nursing Times
8. Eisai Patient Support for LEQUEMBI, Eisai
9. ADvance Website, Biogen
10. Working with pharmaceutical industry, Alzheimer's research UK

Conclusion

Incoming DMTs could transform AD from an inevitable deterioration to a treatable condition

AD is not only a devastating diagnosis for PWD and their family and friends, but also a growing clinical and economic dilemma which will only exacerbate as populations age. DMTs could allow people more symptom-free years to spend time with loved ones, continue working and reduce dependence on health and social care systems.

A fundamental change in the AD care pathway must be realised to fully reap the benefits that DMTs have to offer

This will require a concerted effort from HCPs, patients, caregivers, policymakers, regulators, payers and Pharma to prioritise earlier detection and facilitate access to treatment. We believe the UK should act now to fully leverage the innovations to come.

Contacts

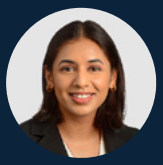
Fiona Thomas, MBChB
Chief Medical Officer
fiona.thomas1@kpmg.co.uk

Adrian Griffiths
Head of Life Sciences, UK
adrian.griffiths@kpmg.co.uk

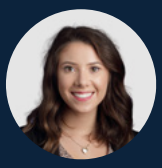
Janak Gunatilleke, MBChB
Head of Health Data and Analytics
janak.gunatilleke@kpmg.co.uk

Guillaume Favier, PhD
Partner, Healthcare and Life Sciences Strategy
guillaume.favier@kpmg.co.uk

Amit Sethi, MBBS
Partner, Integrated Care, and Global Co-lead, Health Equity and Access in Developed Markets
amit.sethi@kpmg.co.uk



Joyeeta Rahman, PhD
Senior Associate, Healthcare and Life Sciences Strategy
joyeeta.rahman@kpmg.co.uk



Helena Szpytman, MRPharmS
Senior Associate, Healthcare and Life Sciences Strategy
helena.szpytman@kpmg.co.uk

Jo Berry
Manager, Operational Transformation, Infrastructure Advisory Group
jo.berry@kpmg.co.uk

Some or all of the services described herein may not be permissible for KPMG audited entities and their affiliates or related entities.

kpmg.com/uk

CREATE: CRT153620A | February 2024