Alzheimer's disease

EU-IN Horizon Scanning Report

November 2024
EMA/540805/2024/Rev. 1

Table of contents

Abbreviations

Aβ: Amyloid beta

AD: Alzheimer’s disease

AI: Artificial Intelligence

APP: Amyloid Precursor Protein

ARIA: Amyloid-Related Imaging Abnormalities

BAF: Business Analysis Forecast

BP: Business Pipeline

CDR: Clinical Dementia Rating

CHMP: Committee for Medicinal Products for Human Use

CSF: CerebroSpinal Fluid

CNS WP: Central Nervous System Working Party

CTIS: Clinical Trials Information System

DMT: Disease-Modifying Treatment

EFPIA: European Federation of Pharmaceutical Industries and Associations

EMA: European Medicines Agency

EMRN: European Medicines Regulatory Network

EU: European Union

EU-IN: European Union Innovation Network

FDA: Food and Drug Administration

IMI: Innovative Medicines Initiative

ISRCTN: International Standard Randomised Controlled Trial Number

ITF: Innovation Task Force

IWG: International Working Group

MAA: Marketing Authorization Application

MCI: Mild Cognitive Impairment

MMSE: Mini-Mental State Examination

MRI: Magnetic Resonance Imaging

NFT: NeuroFibrillary Tangle

NIA-AA: National Institute on Aging-Alzheimer's Association

PET: Positron Emission Tomography

PIP: Paediatric Investigation Plans

PMDA: Pharmaceuticals and Medical Devices Agency

PRIME: PRIority MEdicines

SA: Scientific Advice

USA: United States of America

WHO: World Health Organization

Glossary

Alzheimer's disease (AD): AD refers to an age-related, neurodegenerative disease leading to a progressive cognitive impairment. AD is a continuum starting at the pre-clinical, asymptomatic stage and progressing to full-blown AD dementia. All stages of the disease are characterized by the presence of AD pathology.

Alzheimer's disease (AD) dementia: dementia severe enough to impact daily activities and affecting patients whose brain shows presence of AD pathology.

AD pathology: Aggregation of β-Amyloid (Aβ) and Tau, leading to the deposition of extracellular Amyloid plaques and intracellular neurofibrillary tangles (NFTs), respectively. Although pathophysiological changes observed in AD patients are not restricted to Aβ and Tau deposition, these two pathophysiological elements only are necessary to define AD.

Biomarker: An objective and quantifiable measure of a physiological process, pathological process or response to a treatment (excluding measurements of how an individual feels or functions).

Disease-modifying treatment (DMT): Treatment that arrests or slows down the underlying pathological or pathophysiological disease process(es), as opposed to a symptomatic treatment.

European Medicines Regulatory Network (EMRN): Network comprised of around 50 regulatory authorities for medicines from the 30 European Economic Area countries (27 EU Member States, Iceland, Liechtenstein and Norway), the European Commission and the European Medicines Agency.

Surrogate endpoint: In clinical trials, a surrogate endpoint is a biomarker that predicts the clinical benefit of a specific treatment. Surrogate endpoints can be used to replace clinical outcomes if sufficient evidence has been provided to have shown their validity.

Executive summary

This horizon scanning report describes current status and key emerging trends in the field of Alzheimer´s disease (AD), explores challenges and opportunities related to the development of disease-modifying treatments and suggest recommendations to inform the work of medicines regulators and their stakeholders.

AD is a neurodegenerative disorder responsible for up to 80% of all cases of dementia. In AD patients, biological changes start occurring years to decades before the onset of clinical signs and symptoms. Despite the burden that AD represents for the patients suffering from it, their relatives and the society at large, no treatment has been shown to stop the progression of the disease to date.

A crucial factor hampering the research and development of disease-modifying therapies is the incomplete understanding of the pathophysiological pathways leading to dementia. As new scientific knowledge becomes available, internationally agreed definitions should be refined and the conduct of clinical trials in presymptomatic individuals or clinical trials targeting symptoms that are present across diseases should be facilitated.

Efficacy assessment tools currently used in clinical trials do not have the ideal psychometric properties, especially in patients at early stages of disease. Regulatory guidance should be updated to enable the development of new outcome measures for this population, and to facilitate the investigation of products intended to prevent the onset of symptoms, for example by reaching a consensus on eligibility criteria to define a presymptomatic population.

Diagnosing AD before the onset of clinical signs and symptoms is, in principle, desirable. However, the absence of validated prognostic factors, the anxiety that such diagnosis can induce, and the absence of treatments to prevent or delay the disease in many people need to be taken into consideration. Guidance should be developed on the disclosure of biomarker and genetic test results in a clinical and a research setting, where different parameters apply.

Including the patient's perspective on what is considered a clinically relevant outcome, especially for early Alzheimer's disease is also crucial.

1. Rationale and objectives of the report

Horizon scanning is the systematic examination of information to detect early signs of scientific and technological developments with previously unknown regulatory challenges or public health opportunities. It aims at enabling the European Medicines Agency (EMA) and the European Medicines Regulatory Network (EMRN) to proactively respond to forthcoming challenges and opportunities. EMA conducts horizon scanning in collaboration with experts and groups such as the EU-Innovation Network (EU-IN) [1]. This entails analysing the future of selected topics and reporting their potential impact on the EMRN over the next 3 to 10 years. The reports include recommendations to adapt the EMRN, to minimise regulatory bottlenecks, to support developers and to facilitate innovation reaching patients. Horizon scanning is an underlying action of strategic goals in EMA's Regulatory science strategy to 2025 [2] and the EMRN Strategy to 2025 [3]. Based on the continual screening of abstracts published by major journals and following a consultation of scientific coordination groups of the EMA and EMRN, the topic of Alzheimer's disease (AD) has been selected to conduct a deep dive.

2. Methods and information sources

The report used multiple sources of information:

- Scientific and regulatory articles: A literature search was conducted in Embase database. The first two queries used for the literature search were (but not limited to): 1) 'alzheimer disease' AND 'dementia' AND 'cogniti*' AND 'biomarker*' AND 'challenge*' AND 'diagnos*' for the years 2020 –

2023 and 2) 'alzheimer*' AND 'dementia' AND 'neurodegenerat*' AND 'therap*' AND 'amyloid' for the years 2020 – 2023. In addition to academic literature, information found in grey literature, conference and workshop documents were also used.

- EMA database search included the Innovation Task Force (ITF) meetings, Business Pipeline (BP) meetings, Priority MEdicines (PRIME), Scientific Advice (SA), Qualification opinions, Qualification advice, Paediatric Investigation Plans (PIP) waivers from January 2019 to June 2023 as well as the Business Analysis Forecast (BAF) 2023 to 2025.
- Records on clinical trials were retrieved from the EU Clinical Trial Register, the Clinical Trials Information System (CTIS), the International Standard Randomised Controlled Trial Number (ISRCTN) and ClinicalTrials.gov registry for the years 2003 to 2023 using an analysis script (https://dev.azure.com/euemadev/RSR/_git/2023-hs-ad?path=/analysis.qmd). Data were loaded on October 2023 and last updated in November 2023.
- The current EU development grant landscape was primarily analysed using the Single Electronic Data Interchange Area (SEDIA) and The Community Research and Development Information Service (CORDIS).
- Experts from the EU-IN and Central Nervous System Working Party (CNS WP) commented on all aspects of the report.

3. Introduction

Dementia, or major neurocognitive disorder, is defined as a progressive loss of cognitive functioning which interferes with independence in daily activities, including occupational, domestic or social functioning. It can be caused by a variety of disorders, including neurodegenerative diseases, and may be associated with other symptoms such as depression, anxiety, paranoia, delusions, visual hallucinations or apathy.

Dementia occurs in about 1 to 2% of adults aged less than 65 years old but the prevalence increases with age and reaches 30 to 50% by age 85. As of 2019, dementia was affecting around 11 million people in Europe and 55 million people worldwide [4], [5]. With Europe's ageing population, the number of individuals affected by dementia is expected to reach 19 million by 2050 [4]. Dementia does not only affect the individuals living with it but also has psychological, social and economic impacts for their relatives, their health carers and society at large. It is estimated that societal and economic cost of dementia in Europe will be over €250 billion by 2030 [6]. It thus represents one of the most devastating healthcare problems facing Europe and has been recognized as public health priority by the World Health Organization (WHO) since 2017 [7]. AD is by far the most common form, affecting 60 to 80% of the individuals living with dementia [5], [8]. In AD patients, biological changes start occurring years to decades before the onset of clinical signs and symptoms. During this so-called "pre-clinical phase", AD neuropathology is characterized by the aggregation of two proteins in the brain, β-Amyloid (Aβ) and Tau, leading to the deposition of extracellular Amyloid plaques and intracellular neurofibrillary tangles (NFTs), respectively. As the disease progresses, AD patients further display synaptic abnormalities, neuronal death, cognitive decline and memory impairment. At this clinical stage, two phases are distinguished. First, the prodromal AD, also referred to as mild cognitive impairment (MCI), is characterized by impaired cognitive abilities without loss of independent functioning. It is followed by "AD dementia", corresponding to the mild, moderate or severe loss of independent social and occupational functioning due to cognitive impairment (Figure 1) [9], [10], [11], [12].

Figure 1. Progression of AD

The most common form of AD, called "sporadic AD", is a complex, multifactorial disease and represents about 99% of AD cases. Autosomal dominant AD, accounting for the remaining 1% of AD cases, is caused by mutations in the genes encoding for the Amyloid Precursor Protein (APP), Presenilin1 or Presenilin 2. Other forms of age-related neurodegenerative dementia include Lewy body dementia, frontotemporal dementia and Parkinson disease-related dementia. As with AD, the aetiology of these neurodegenerative dementias is multifactorial and many underlying mechanisms such as neuroinflammatory, neurovascular, metabolic or genetic factors are found in these dementias [13]. The large majority of patients suffering from dementia present mixed dementia, i.e. suffer from at least two forms of dementia [8]. Despite the burden that AD and other dementias represent, no treatment has been shown to stop the progression of clinical signs and symptoms to date.

Although a number of challenges, opportunities and recommendations provided in this report apply to age-related dementias at large, this horizon scanning report specifically focuses on AD.

4. Current status and key emerging trends

4.1. Current diagnosis

Detecting and diagnosing AD as early as possible allows early intervention for secondary prevention that may become available. However, diagnosing AD is challenging due to its gradual onset starting with a pre-symptomatic phase with no clear clinical manifestation despite neuropathological changes. In addition, the proportion of mixed dementia dramatically increases with age, which complicates the diagnostic. The three following sections describe the current guidelines for the diagnosis of AD in a research setting and in clinical practice, and provide an overview of the neuropsychological tests and biomarkers most widely used in both settings. Diagnosis and treatment of co-morbid medical conditions other than dementias such as depression and sleep disturbance are excluded from this report.

Guidelines

AD diagnosis in clinical practice and in a research setting have been following different guidelines until now.

Guidelines for the diagnosis of AD in a clinical setting are provided by the European Federation of the Neurological Societies [14] and various national guidelines. The core diagnosis remains based on the presence of a gradual cognitive impairment using a battery of neuropsychological tests allowing the evaluation of memory, executive functions, language, praxis and visual-spatial abilities. Exclusion of aetiologies other than AD should also be performed (patient's medical history, screening of possible co-morbidities). If the evaluation by the practitioner indicates a mild cognitive impairment**,** biomarkers measured by imaging, electroencephalography (EEG), cerebrospinal fluid (CSF) analysis or genetic testing at specialised and tertiary care centres may confirmed mild cognitive impairment is due to AD [14], [15].

For research purposes, AD diagnosis was originally based on the presence of both clinical cognitive impairment and post-mortem histopathological features, referred to as AD pathology in this report (presence of Amyloid plaques and neurofibrillary tangles in the neocortex and hippocampal formation) [16], [17]. The availability of imaging methods, and the observation that biological changes start occurring 10 to 20 years before the onset of clinical signs and symptoms led to revise the research diagnostic framework in order to cover the early asymptomatic phase of AD. In 2007 and 2011 respectively, the International Working Group (IWG) and the National Institute on Aging-Alzheimer's Association (NIA-AA) included the detection of biomarkers in the diagnostic [10], [11], [12]. Currently, both IWG and NIA-AA sets of criteria are accepted by the EMA guideline on clinical studies for AD medicines in effect since 2018 [18]. More recently, the NIA-AA adopted a pure biological definition of AD, shifting the diagnostic towards a pure biomarker-based diagnosis [19], [20]. This guideline was updated in 2023, following the development of plasma biomarkers and the first two marketing authorizations of disease-modifying treatments by the Food and Drug

Administration (FDA) (see section 4.3) [21]. The document aims to provide criteria for AD diagnosis and staging to be used across clinical and research settings [22].

Currently neuropsychologic tests: cognitive, behavioural and functional assessments

In a clinical setting, cognitive screening tests are used to identify patients at risk who require a more detailed investigation. The two most widely used screening tests are the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment. Other tests include the Memory Impairment Screen, the Clock Drawing Test and the verbal fluency. A more in-depth assessment further aids the diagnosis of AD by objectively assessing memory, executive functions, language, praxis and visual-spatial abilities.

In a research setting, the choice of neuropsychometric tests depends on the context of use and the stage of the disease [18]. Several assessment tools are usually used as no ideal neuropsychological test exists at present. According to our search in the four clinical trial databases EU Clinical Trial Register, CTIS, ISRCTN and ClinicalTrials.gov registry from January 2003 to June 2023, the MMSE score and the clinical dementia rating (CDR)-Global scores are often used as inclusion criteria in clinical trials, whereas the cognitive subscale of the AD Assessment Scale (ADAS-Cog), the CDR-Sum of Boxes and different versions (depending on the stage studied) are widely used as primary or co-primary endpoints as the scale covers both effects on cognition and function.

Recently, an AI-based digital diagnostic tool for the remote measurement of cognitive function, CognICA, completed its registration as a medical device in the EU, Canada, United Kingdom and United States of America (USA) among others. The device is intended for the detection of dementia in both clinical and research settings.

Current biomarkers

Biomarkers are pivotal in AD diagnosis, enabling the detection of disease pathology before the onset of clinical signs and symptoms. They have potential to predict disease progression and to monitor a treatment effect. Biomarker acceptance by regulators, or biomarker qualification, facilitates the use of these biomarkers in a clinical trial setting for a defined context of use [23]. Six potential contexts of use can be distinguished for biomarkers in drug development: 1) diagnostic biomarkers, to detect or confirm the presence of AD or identify the subtype of AD; 2) enrichment biomarkers, to select patient populations; 3) prognostic biomarkers, to determine the progression rate of the disease in AD patients; 4) predictive biomarkers, to predict a future clinical response to therapy and for safety assessment; 5) pharmacodynamic biomarkers to determine whether a biological response has occurred in an individual who has been exposed to a medical product; and 6) surrogate biomarkers to measure a treatment effect in absence of clinically-observable changes.

The table below summarizes the most widely used biomarkers in clinical trials as inclusion criteria or outcome assessment tools in 2022 [24]. Looking at the four clinical trial databases (EU Clinical Trial Register, CTIS, ISRCTN and ClinicalTrials.gov registry) from January 2003 to June 2023, biomarkers as inclusion criteria have been increasingly used in clinical trials with a phase 3 label, i.e. phase 2/3 and phase 3 clinical trials, in the past 20 years. The use of biomarkers as primary endpoints started only in 2012 with a clear increase can be since 2020. So far this has been mainly limited to phase II studies where their use as primary endpoint in confirmatory registry for approval is at discussion. As of today, EMA has only qualified enrichment biomarkers (see Annex 2).

Source	Biomarker	Regulatory qualification/approval
CSF	**Amyloid** (Aβ42 alone or measured as a ratio with Aβ40, total tau, or p-tau)	EMA qualification as enrichment biomarker
	Tau (Total Tau or p-Tau)	EMA qualification as enrichment biomarker
Imaging	**Amyloid PET**	EMA qualification as enrichment biomarker EMA approval of Amyvid (Amyvid | European Medicines Agency (europa.eu)), a radioactive (^{18}F) diagnostic tool for PET imaging EMA approval of Vizamyl (Vizamyl | European Medicines Agency (europa.eu)), a radioactive (^{18}F) diagnostic tool for PET imaging EMA approval of Neuraceq (Neuraceq | European Medicines Agency (europa.eu)), a radioactive (^{18}F) diagnostic tool for PET imaging
	Tau PET	FDA approval of Tauvid (https://www.fda.gov/media/140343/download), a radioactive (^{18}F) diagnostic tool for aggregated Tau NFTs PET imaging
	MRI hippocampal atrophy	EMA qualification as enrichment biomarker
	^{18}F-FDG PET hypometabolism	-
Plasma	**Amyloid**	-
	Tau	-

Table 1. Most widely used biomarkers for AD diagnosis in a research setting.

Regarding the clinical practice, CSF analysis and positron emission tomography (PET) imaging for Aβ and Tau are usually used at specialised and tertiary care centres but their availability varies greatly according to the region [15], [25].

4.2. Biomarker development horizon

Public scientific literature and EMA databases (ITF briefing meetings, BP meetings, SA, PIP waivers, Committee for Medicinal Products for Human Use (CHMP) qualification opinions and CHMP qualification advice) were reviewed and analysed to identify trends in research and development. Current research mostly aims at identifying biomarkers that are sensitive and able to detect features of the pathophysiologic processes before symptom onset. In addition, these biomarkers would ideally need to be inexpensive, minimally invasive and scalable. Although acceptance of biomarkers by regulatory authorities depends on their context of use, at the "pre-regulatory" research stage, the context of use is not yet specified by developers (see part 6.3).

CSF and peripheral fluid biomarkers

Peripheral fluid biomarkers, in particular blood or plasma tests, are gaining significant interest as they are easily accessible and require a less complex training by health care professionals than a lumbar puncture while being cheaper than PET scan or magnetic resonance imaging (MRI) [26], [27]. Detecting biomarkers in the plasma or other peripheral fluids is usually more challenging than in CSF, as blood-brain barrier prevents

molecules from freely passing from the central nervous system to the blood, resulting in low biomarker concentrations [28]. Promising blood, plasma and other peripheral biomarkers are listed below [29]. This list can be applied to promising CSF biomarkers, except for plasma Aβ and Tau that are already well established as CSF biomarkers (see table 1).

- Plasma Aβ - Its clinical use has been hampered by the high variability of the results as well as by the very low basal plasma concentrations. The use of Aβ 1-42/ Aβ 1-40 ratio shows positive correlation with amyloid PET and decreases the intra-patient variability.
- Plasma Tau - While Tau can be used as marker for any tauopathies and pathologies associated with neuronal death, specific phospho sites are more specific to AD (e.g. ^{181}P-Tau).
- Markers of neurodegeneration - In particular Neurofilament Light (NFL) chain protein is a marker of axonal degeneration that shows promising results. Although not specific, markers of neurodegeneration seem to show a good correlation with disease progression, if used in an age-specific manner. Markers for synaptic pathology such as growth-associated protein 43 (GAP-43), SyNaptosomal-Associated Protein 25 (SNAP-25), Synaptotagmin-1 and Neurogranin, also seem to be promising biomarkers for brain degeneration and cognitive impairment [30].
- Markers of neuroinflammation - In particular, Glial Fibrillary Acidic Protein (GFAP), the main marker of astrogliosis, is detected in higher amount in AD patients compared to healthy subjects and correlate with cognitive impairment. Triggering Receptors Expressed on Myeloid cells 2 (TREM2), a marker of microglial activation, is another promising biomarker for early detection of AD and progression [31].
- miRNAs - miRNA are small (19 to 24 nucleotide-long) non-coding RNAs that serve as regulators of gene expression. Between 50 and 70% of miRNA have been identified in the central nervous system, but circulating miRNAs are also found in the CSF, plasma, urine and saliva [32], [33]. They can regulate multiple signalling pathways in response to pathophysiological stimuli and target key disease genes associated with neurodegenerative or neuroprotective effects, inflammation, lipid metabolism or mitochondrial function. The expression profile of miRNAs in patients suffering from MCI shows a correlation with AD-related genes such as BACE1 and APP, indicating that they could be exploited as fluid biomarkers or therapeutic targets of early-stage AD.
- Epigenetic profile - DNA methylation profile of blood samples as a method to measure biological age, are under development for AD in particular. E.g. DunedinPACE biomarker [34], [35].
- Exosomes - Exosomes are lipid compartments that allow the translocation of biological substrates such as proteins, lipids and miRNA, from one cell to another [36]. Exosomes are released by all cell types, including neurons and astrocytes, and have the ability to penetrate the blood brain barrier, allowing the analysis of neuron-derived exosomes by blood sampling. High-sensitivity assays are commercially available at a relatively low cost. The diversity of substrates contained in each exosome offers a unique opportunity to analyse a combination of targets of different types. Further research is needed to identify individual or groups of substrates from exosomes that consistently predict cognitive impairment and validate them as sensitive and specific markers.
- Oral microbiome – The oral microbiome is altered in AD patients, with for instance *V. parvula* and *P. gingivalis* being predominant in AD patients. Profiling the oral microbiomes in patients with AD or cognitive impairment in general represents a strategy for the identification of potential biomarkers, as seen by the sudden increased number of publications related to 'oral microbiome' and 'Alzheimer' since 2020 when searching in Embase.

The use of -omics, will also allow the identification of additional targets. Various types of markers, e.g. lipid metabolites, amino acids, metals and oxidative stress markers have further been identified [37], [38].

Biomarker-targeting sensor platforms are being developed in academic laboratories. Their translation into clinical analytical platforms will be crucial for the development of sensitive peripheral fluid biomarkers [39].

Imaging biomarkers

- Magnetic resonance texture analysis for the detection of Aβ and Tau proteins - The current pixel resolution of MRI does not allow the detection of Aβ plaques and NFTs. Their presence, however, changes the pixel intensity of MRI images that can be captured by an emerging image analysis, the texture analysis. MRI texture analysis could be used to develop new neuroimaging biomarkers [40].
- PET imaging to capture synaptic function - The use of PET ligands to measure synapse has been recently established with the synaptic vesicle glycoprotein 2A (SV2A) PET ligands [^{11}C]UCB-J [41], [42]. Similar to fluid biomarkers for synaptic degeneration, synaptic labelling has the potential to be a strong indicator of brain degeneration and cognitive status.

Retinal biomarkers

The retina belongs to the central nervous system and is easily accessible. Investigating the structural changes occurring in the retina and the retinal microcirculation using tools such as optical coherence tomography and optical coherence tomography angiography might represent a target for early diagnosis of dementia [43], [44], [45].

Vocal biomarkers

Subtle changes in voice and language can be detected years before the appearance of prodromal signs and symptoms of AD [46], [47]. Vocal signs include pitch variation and modulation, slow speech rate and hesitation and loss of semantic ability. With the development of voice technologies such as vocal assistants on smartphones, voice features have the potential to become a non-invasive biomarkers for the early diagnosis of dementia [48].

Digital tools

Digital technologies are increasingly being harnessed as innovative tools for the diagnosis of AD. In the EMA internal databases analysed, multiple innovative digital tools were identified in a wide range of AD diagnostic applications. They are classified below according to the role they could play in AD diagnosis, in order of importance:

- Digital tools to automatically and remotely analyse tests that are not intrinsically digital (e.g. the digital clock drawing).
- New digital measurements, e.g. digital measures of sleep patterns or fatigue.
- The use of digital tools to replace the clinician, including during the interview (automatic and digital sampling/analysis + virtual clinician).

4.3. Current treatments

Currently, four small molecules hold a marketing authorization for the treatment of AD in Europe. Three acetylcholinesterase inhibitors are indicated for the treatment of mild to moderate AD: Donepezil and Galantamine, approved through the European mutual recognition procedures since 1997, and Rivastigmine, approved in 1998 through the EMA centralized procedure [49]. The 4th treatment, Memantine, is a NMDA receptor antagonist approved in 2002 for the treatment of moderate to severe AD [50]. These four treatments temporarily improve cognition but none of them prevents or delays the progression of the underlying disease process.

Disease-modifying treatment (DMT) are treatments that arrest or slow down the underlying pathological or pathophysiological disease process(es) [24]. At the time of the report's drafting, the EMA adopted for the first time a positive opinion on the marketing authorization of a DMT, the monoclonal Aβ antibody Lecanemab [57]. The recommendation of Leqembi is based on a slower cognitive decline in patients suffering from MCI or mild AD dementia and who have only one or no copy of ApoE4. In addition, a marketing authorization application (MAA) is currently under evaluation for the Aβ antibody Donanemab-azbt. In the USA, two DMTs have been approved by the FDA via the Accelerated Approval Program based on the surrogate endpoint of reduction of Aβ plaque in the brain: Aducanumab in June 2022 (discontinued by its manufacturer in 2024) and Lecanemab in January 2023 [51], [52]. The accelerated approval pathway requires the company to verify clinical benefit in a post-approval trial. In June 2023, Lecanemab's accelerated approval was converted to a traditional approval based on the results of a study (ClinicalTrials.gov ID: NCT03887455) confirming the clinical benefit of the product [53]. In July 2024, the FDA further granted a full marketing authorization to Donanemab-azbt, based on a reduction of cognitive decline [54].

4.4. Medicine development horizon and anticipated timeframe for regulatory interactions

Treatments in clinical trials

An overview of the number of ongoing clinical trials for AD and MCI registered since 2005 in the four databases investigated is provided in the figure below (Figure 2). Taking into account the phases of the clinical trials, there seems to be a steady number of newly started phase 1 and/or 2 clinical trials each year in the past 20 years, with a slight increase since 2019 (Figures 2B and 3). No clear trend appears in the number of newly initiated phase 3 clinical trials.

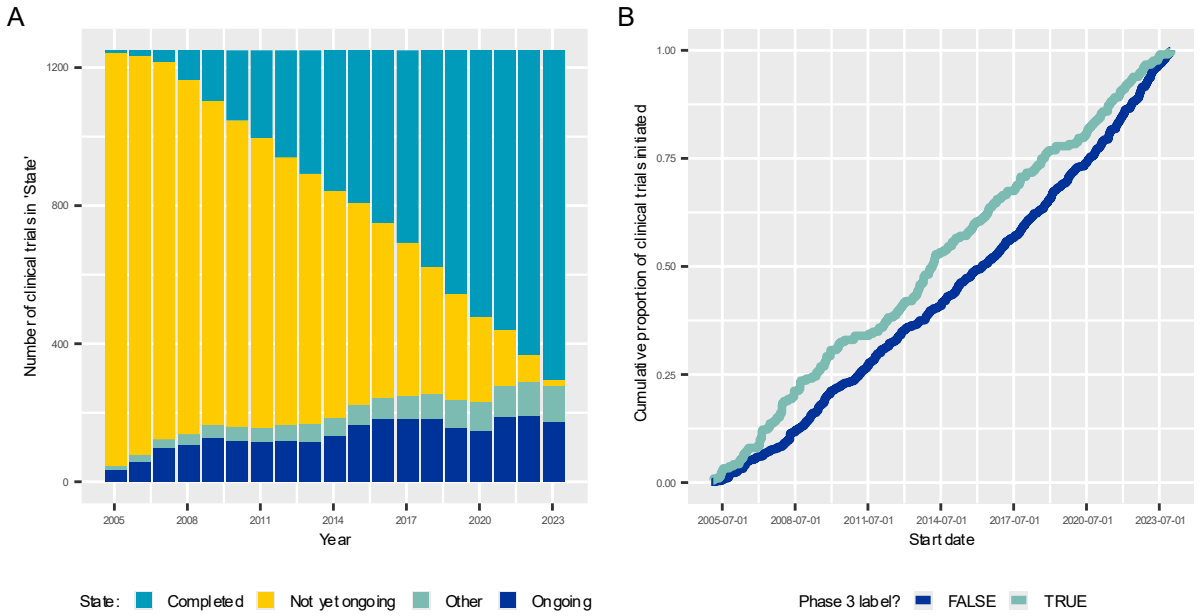

Figure 2. Exploratory analysis of the clinical trials investigating treatments intended for AD or MCI registered in CTGOV, EUCTR, CTIS or ISRCTN since 2005.
Panel (A) shows ongoing clinical trials. "Ongoing" clinical trials are "Recruiting", "Active", "Ongoing", "Ongoing, recruiting", "Active, not recruiting", "Authorised, not started", "Enrolling by invitation", "Not yet recruiting", "Temporarily Halted" or "Started". Status "Completed" (light blue) indicates clinical trials described as "Completed", "Prematurely ended", "Terminated" or "Ended". Status "Not yet ongoing" (yellow) comprises "Planned", "Not yet authorised" or "Not yet started" clinical trials. "Other" (green bars) indicates clinical trials with an unknown status, for which the status could not be calculated, withdrawn clinical trials, suspended clinical trials, clinical trials that were prohibited by the competent authority or that were no longer

available. Not all clinical trials labelled as phase 1 are registered in the four public registers.
Panel (B) shows the rate of newly initiated clinical trial. When focusing on phase 1 or 2 clinical trials (i.e. clinical trials that do not have a "phase 2/3" or "phase 3" label, dark blue line), it seems that they have been regularly initiated since around 2008, with a potential increase since 2020 that would merit further monitoring before drawing conclusions (upward inflection).

In the following section, data from the yearly reports from Cummings *et al* were analysed, with a focus on year 2023, to get an overview of the treatments currently in phases 1, 2 and 3 clinical trials [24]. In January 2023, 141 treatments for AD or MCI attributed to AD in 187 trials were registered in ClinicalTrials.gov, among which 31 were in phase 1, 87 in phase 2 and 36 in Phase 3 trials (Figure 3, year 2023). The authors distinguished symptomatic treatments, i.e. "treatments whose purpose is cognitive enhancement or control of neuropsychiatric symptoms without claiming to impact the underlying biological causes of AD", versus DMTs, i.e. "Treatments intended to change the biology of AD and slow the course of the disease". When the sponsor did not specify the therapeutic purpose, authors used the features of the trial such as clinical outcomes, trial duration and use of biomarkers as outcomes to distinguish between symptomatic treatments and DMTs. Among the 141 treatments, the large majority (79%) are DMTs. Similar to the preclinical research, AD medicines under clinical trial investigation comprise a range of targets and mechanisms of action. Among the 111 DMTs, 17% target inflammation, 16% Amyloid, 13% synaptic plasticity/neuroprotection and 9% Tau. Other targets include metabolism and bioenergetics, oxidative stress and proteostasis. Of note, biologics under investigations include the following mechanisms of action:

- 5 stem cell therapies (2 in phase 1, 3 in phase 2) and 1 autologous natural killer cells in phase 1;
- 2 anti-Tau antisense oligonucleotide (1 in phase 1 and 1 in phase 2); 1 Adeno-Associated Virus (AAV)-mediated human APOE ε2 cDNA in phase 1 and 1 RNAi targeting APP mRNA in phase 1;
- 4 active immunotherapies targeting Aβ (2 in phase 1 and 2 in phase 2) and 1 active immunotherapy targeting Tau in phase 1.

In addition, the pipeline contains for the first time a psychedelic, Psilocybin, currently in phase 1.

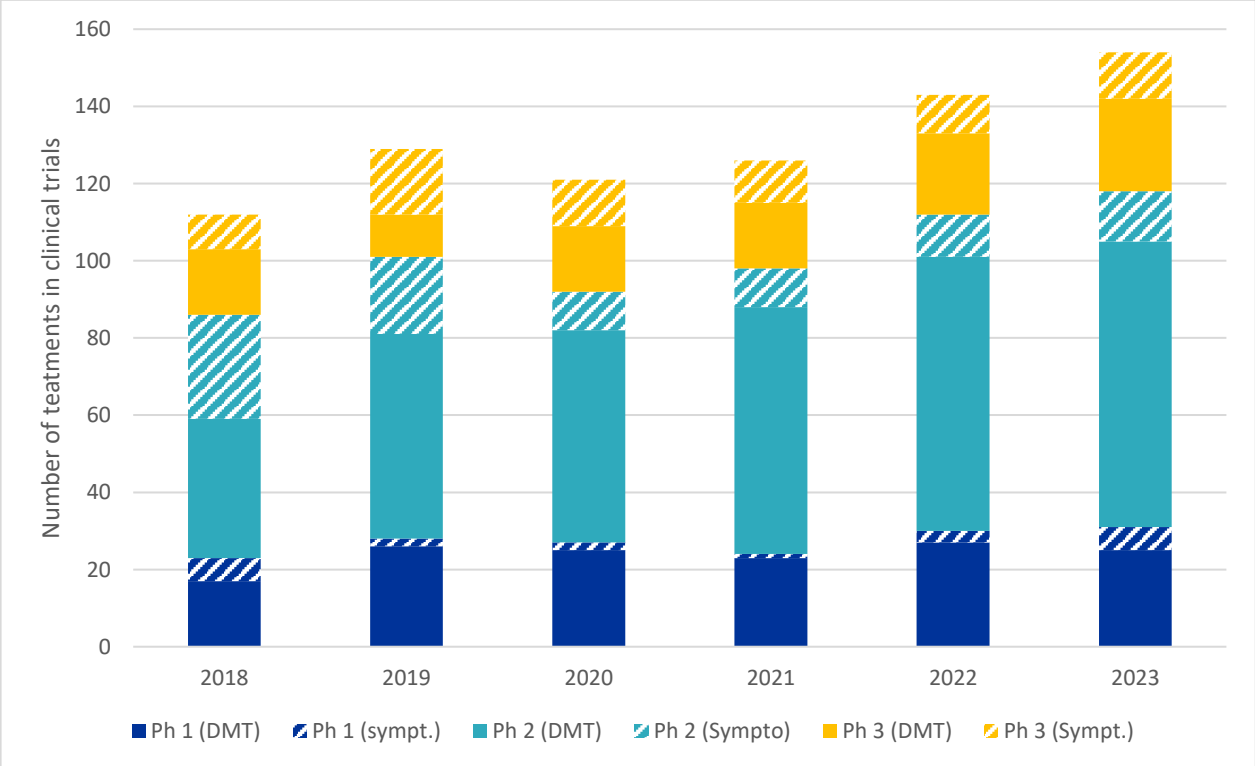

Figure 3. Treatments intended for AD or MCI attributed to AD registered in phases 1, 2 and 3 in ClinicalTrials.gov from January 2018 to January 2023.
Trials labelled as "recruiting", "active but not recruiting", "enrolling by invitation" and "not yet recruiting" were included. Trials designated as phases 1/2 or 2/3 were included in phases 2 and 3, respectively. Dark blue bars represent the treatments in phase 1, light blue bars in phase 2 and yellow bars in phase 3 clinical trials; hatched bars represent the symptomatic investigational medicines and solid bars the DMTs. Data were extracted from the last 6 yearly reports from Cummings *et al*. [24], [58], [59], [60], [61], [62].

EMA interactions

- **BP meetings (Jan 2019 – June 2023)**: Out of the 67 BP meetings, 9 were dedicated or tackled challenges related to the development of AD treatment such as transdiagnosis approach, patient-reported outcomes, use of surrogate biomarkers and validation of digital biomarkers. During these 9 meetings, a total of 10 treatments were presented as part of the companies' pipeline: 1 treatment targeting a phosphodiesterase indicated for cognitive dysfunction across psychiatric and neurological diseases, 6 treatments targeting Aβ or related enzymes (4 anti-Aβ monoclonal antibodies, 1 bispecific Anti-Aβ /transferrin monoclonal antibody and 1 γ-secretase modulator), 4 products targeting Tau or related enzymes (2 monoclonal antibodies, 1 O-GlcNAcase inhibitor preventing Tau phosphorylation and 1 Tau antisense oligonucleotide).
- **PIP waivers (Jan 2019 – June 2023)**: 1 already identified in SA (anti-Aβ).
- **SA (Jan 2019 – June 2023)**: 20 SA related to products intended for pre-clinical AD, MCI due to AD or AD were provided. Among these 20 treatments, 7 targeting Aβ (5 Aβ antibodies, 1 β-Site amyloid precursor protein cleaving enzyme (BACE) inhibitor and 1 active immunotherapy aiming at stimulating the production of antibodies targeting Aβ42 oligomers), 5 targeting Tau (2 antibodies, 2 protein kinase inhibitors and 1 inhibitor of Tau aggregation), 2 targeting synaptic transmission, 1 the metabolism, 1 plasmapheresis, 1 being a bacterial proteases and 2 having mixed activities and targets.
- **PRIME (Jan 2019 – June 2023)**: 6 PRIME critical summary reports on AD treatments were found among which 4 targeting Aβ (3 monoclonal Ab and 1 glutaminyl cyclase (QC) inhibitor), 1 the gut-brain axis (oligosaccharides) and 1 the hypothalamic-pituitary-adrenal axis (enzyme inhibitor reducing the activation of inert cortisone into cortisol). The 6 PRIME applications were denied.
- **ITF briefing meetings (Jan 2019 – June 2023)**. Out of the 174 ITF briefing meetings that took place between January 2019 and June 2023, only 2 were dedicated to the development of a treatment indicated for MCI due to AD or AD dementia. The first meeting was dedicated to a phase 2a clinical trial exploring the efficacy of a free radical scavenger targeting neuroinflammation, oxidative stress, neurotoxicity and Amyloid plaque. The second therapy was a gene therapy viral vector (AAV9) encoding for E2F Transcription Factor 4 and acting as a cell cycle regulator.

On going fundamental and pre-clinical research

Literature search performed in Embase and ADIS Insight indicates that the majority of fundamental and pre-clinical research focuses on **protein regulation,** in particular on:

- Extracellular protein clearance and inhibition of protein aggregation - Much of the research focuses on immunotherapies targeting Aβ and Tau, including AAV-mediated RNA encoding anti-Tau or anti-Amyloid antibodies, and RNA inhibitor-based therapies. Protein kinases, which are particularly important in Tau hyperphosphorylation and the formation of neurofibrillary tangles, represent another potential target [63].
- Protein degradation and extracellular clearance - Examples of development found in ADIS Insight include transcription factor modulators allowing autophagy activation and prevention of protein aggregation (https://adisinsight.springer.com/drugs/800039496) and small molecules engaging

pathological Tau aggregates to the ubiquitin-proteasome system for further degradation (https://adisinsight.springer.com/drugs/800069330).

- Protein inhibitors involved in Amyloid degradation, e.g. Amyloid precursor protein secretase modulator that reduces the production of toxic amyloid-beta protein Aβ42 (https://adisinsight.springer.com/drugs/800054369).

Another important area of research is **neuroinflammation**:

- An increasing number of articles focus on the role of the immune system - examples of compounds under development are inflammasome inhibitors (https://adisinsight.springer.com/drugs/800047350), cytokine inhibitors (https://adisinsight.springer.com/drugs/800046475) and glial cell and macrophage modulators (https://adisinsight.springer.com/drugs/800055685).
- The role of gut/brain axis in AD pathogenesis is also being increasingly explored (LB P4 - AdisInsight (springer.com)).

Other important targets include the **metabolism and mitochondrial dysfunction**:

- Examples include proteins targeting mitochondrial membrane transport (Alzheimer's disease therapeutic - MPC Therapeutics - AdisInsight (springer.com)) and mitochondrial protein stimulants (ND 108E - AdisInsight (springer.com)).

In order to promote **neuroprotection**, three main approaches are taken:

- Cell therapies, e.g. spinal cord-derived stem cells differentiated into human neurons and glia (https://adisinsight.springer.com/drugs/800025566).
- Mesenchymal stem cells-derived secretome seems to arise as a strategy to avoid side effects due to allogenic cell transplantation [64].
- Nerve growth factor stimulators.

Other targets comprise **metal ion imbalance**, including the cell death pathway ferroptosis, **oxidative stress**, **vascular dysfunction** and **neurotrophic factors**. Besides small molecules and biologicals targeting the aforementioned pathways, research on deep-brain stimulation, transcranial magnetic stimulation and transcranial electrical stimulation are ongoing.

5. Regulatory preparedness

5.1. International initiatives

Public health policies/projects

Dementia is a major cause of disability and dependency among older people, affecting more than 55 million people worldwide [5]. AD has been widely recognized as the most common cause of dementia since the early 1980's and with Europe's ageing population, the prevalence of AD is expected to double in the next 30 years [65]. Because of this there has been a constant and increasing interest in the disease amidst the scientific community and community in general [66]. Examples of ongoing scientific initiatives include the international clinical studies for the prevention of clinical decline led by the FINGERS Brain Health Institute, which builds on the FINGER study [67], [68], or the Australian Imaging, Biomarker and Lifestyle study [69], an observational cohort study focused on the onset and progression of AD. This interest in AD is shared by major stakeholders like countries and large private entities which have recognised the need for further policies and investments on every facet of AD and dementia research [70], [71], [72], [73]. In the last decade multiple institutions have launched long-term projects to directly assess the challenges related to AD

and dementia, most notably the Global action plan on the public health response to dementia 2017-2025 adopted by the WHO [7], the USA's National Plan to Address Alzheimer's Disease [74] and the World Dementia Council holding global dialogues [75].

Regulatory initiatives

On a regulatory perspective, the United States FDA and the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) have issued guidance documents on the topic:

- Draft guidance for industry "Early Alzheimer's Disease: Developing Drugs for Treatment" (issued in February 2018) [76]. This guidance updates the last draft guidance issued in February 2013 [77] on aspects of drug development at the early stage of AD.

- Guidance for industry "Human Gene Therapy for Neurodegenerative Diseases" issued in October 2022 [78].

Another important initiative is the Critical Path for Alzheimer's Disease, created in 2008 to enhance regulatory decision-making tools and accelerate therapeutic innovation in AD [79]. This global and multi-stakeholder initiative is currently leading the Tau-PET Harmonization Working Group, the Tau-PET Surrogacy Working Group and the Quantitative Modeling Working Group.

5.2. European initiatives

Public health policies/projects

At EU level, a number of EU-funded joint programs have been undertaken in the last 10 years. The last ones, the European Prevention of Alzheimer's Dementia Programme [80], [81] (ended in 2019), the European Dementia Prevention Initiative [82] (ended mid-2023) and the EU's Joint Programming on Neurodegenerative Diseases [83], mostly focus on research on AD prevention, but also include work on AD research at large and on the social care and structures adapted to AD patients and their relatives. The European Brain Council, in collaboration with the European Federation of Pharmaceutical Industries and Associations (EFPIA), further initiated "RETHINKING Alzheimer's disease", a project aiming at developing policy recommendations touching upon detection, diagnosis and management of the disease [15], [84]. Finally, the European Academy of Neurology Guideline Production Group listed the update of the "Guideline for the diagnosis and management of Alzheimer's Disease" [14] as a priority topic 2022-2024 [85].

While EU projects are crucial to dementia research, ongoing call for actions and grants remain the main opportunities and drivers of progress in these fields. Since January 2013, the EU has published a total of 41 grants concerning neurodegenerative diseases, 32 specifically related to AD and dementia (see annex), 2 of which are still open for submission under three different programmes, EU4Health Programme, Horizon 2020 Framework Programme (H2020 - 2014-2020), which includes the 2 versions of the Innovative Medicines Initiative (IMI1 & IMI2), and H2020 successor, Horizon Europe (HORIZON).

A look at the results in the annex 2 "List of EU grants for neurodegenerative research since 2014" shows the continued effort of the EU in promoting and nurturing initiatives that assess all the various aspects of neurodegenerative diseases, particularly AD and dementia. These range from platform-based projects for early screening to research concerning the development of treatment and identification of biomarkers to even palliative care for terminal patients. It is also interesting to see how throughout this period the identification of biomarkers and early onset symptoms have remained the two most consistent topics, and except for international infrastructure establishment, the two most financed.

Regulatory initiatives

Since 2004, medicinal products for human use containing a new active substance and intended for the treatment of neurodegenerative disorders fall under the mandatory scope of the centralized procedure.

In February 2018, the EMA adopted the "Guideline on the clinical investigation of medicines for the treatment of Alzheimer's disease" [18].

Besides, the CNS WP, set up by the CHMP in 2022, carries out tasks such as providing product-related support upon request from EMA committees and working parties, preparing, reviewing and updating guidelines and concept papers and providing trainings and workshops to assessors. Two long-term goals set-up in their 3-year workplan 2022 to 2024 directly impact AD drug development [86]. The first one is the development "of consistent principles for feasible, efficient and robust data generation in the asymptomatic phase of neurodegenerative disorders". The second one consists in preparing the expert network for both the challenges and opportunities in situations when disease definitions are uncertain and subject to change. In particular, the need of clear regulatory views on transdiagnostic and/or symptom specific indications is acknowledged.

6. Challenges and opportunities

6.1. Limited understanding of AD pathophysiology

Current status and challenges

A major factor hampering the development of DMTs is the lack of understanding of the pathophysiological pathway leading to AD dementia. AD is a complex, multifactorial disorder associated with a variety of comorbidities and risk factors, e.g. diabetes, obesity, metabolic syndrome and apolipoprotein E (APOE) ε4 genetic variant. Neuropathological hallmarks of AD include the deposition of Amyloid plaques and neurofibrillary tangles, and neuroinflammation. As the disease progresses, brains further display synapse and neuronal loss and cerebral atrophy. The relationship between inflammation, Aβ deposit, Tau pathology and the onset and progression of symptoms is, however, not yet fully understood. In the last 30 years, much of the research has been based on the amyloid hypothesis, stating that the deposition of Aβ peptide in the brain parenchyma is the causative agent of the neuropathological process ultimately leading to AD dementia [87]. This hypothesis is, however, still under debate among the scientific community [88], [89]. From a regulatory perspective, the FDA and EMA adopted a different approach. Whereas the FDA considered, in the context of the accelerated approvals of the two Aβ-directed antibodies Aducanumab and Lecanemab (later converted to standard based on clinical endpoints), that Amyloid reduction is "reasonably likely to result in a clinical benefit for patient", the EMA considered that amyloid reduction is not an established surrogate for efficacy [18], [55]. Further research needs to be performed to better understand the etiology of AD and the interplay between Aβ deposit, Tau pathology, neuroinflammation and other factors in the onset and progression of clinical signs and symptoms.

Related to the lack of understanding of the pathophysiology, a clear, universal definition of AD is lacking. Since the first guideline on AD diagnosis based on clinical and histopathologic criteria [16], the definition of AD has significantly evolved due to scientific advances and the evolution of society standards. In 2018, the NIA-AA Research Framework shifted the definition of AD from a syndromal to a biological construct [19], [22]. Despite the current lack of understanding on the neuropathological changes leading to cognitive symptoms, it is generally accepted that the neuropathological changes necessary to define AD, called in this report "AD pathology", are restricted to Amyloid plaques and neurofibrillary Tau deposits [19], [90], [91], [92]. In the absence of demonstrated causality between AD pathology and development of cognitive deficits, and considering that a significant subset of patients with AD pathology do not develop dementia [93], [94], this definition presents two major limits. First, we cannot predict whether and when a patient with AD pathology will develop dementia. Second, in patients with cognitive deficit, suffering from a dementia other than AD and presenting AD co-pathology, symptoms can be misattributed to AD.

Opportunities

- Research should be conducted on the pathophysiological pathway(s) leading to dementia. Once research has successfully determined the underlying disease pathways for dementia, including AD dementia, there will be opportunities for new biomarkers and DMTs. This will also allow the adoption of a universal definition of AD.
- Sharing studies, datasets and biosamples from patients with inherited AD should be encouraged in order to provide insights on the asymptomatic phase.
- Considering the proportion of mixed dementia diagnosed and the overlap in the neuropathological characteristics (e.g. protein misfolding and accumulation) and risk factors between neurodegenerative diseases, data sharing and analysis across disease areas should be encouraged. In particular, analysis of large-scale data sets should help to better comprehend the different mechanisms leading to dementia across neurodegenerative diseases (<20% of consortia share their data [95]).
- The conduct of basket trials and the adoption of a 'trans-diagnostic' or 'disease-agnostic' treatment approach in the frame of a clinical trial should allow the development of therapeutics treating the cause of dementia across neurodegenerative diseases. AD is a multifactorial disorder associated with a variety of risk factors and comorbidities. In addition, many pathophysiological changes and causal mechanisms leading to AD are overlapping across neurodegenerative dementia (e.g. Tau misfolding and accumulation are a hallmark of both AD and frontotemporal dementia) - and more generally across age-related neurodegenerative diseases (e.g. neuroinflammatory, metabolic, neurovascular and genetic factors). Shifting the indication from a syndrome diagnosed using classical diagnostic tools such as the DSM-5 (e.g. "MCI due to AD", "AD dementia" and "Frontotemporal dementia") to a symptom linked to an identified pathophysiological mechanism, independently of the current disease definition (e.g. dementia linked with/due to misfolded Tau), might allow the development of biomarkers and DMTs targeting the cause of a symptom present across disorders.

6.2. Animal models poorly translate into human disease

Current status and challenges

Despite the number of programs for the development of AD therapy, therapeutic options are limited. The failure of clinical trials can be partly explained by the poor translatability of animal models for AD to human disease. Alzforum listed more than 200 animal models for AD, most of which are based on human genetics [96]. While these models have been valuable to better understand the pathophysiology of AD, they poorly translate into the human disease. Indeed, although these models present cognitive deficits and Aβ accumulation, they only develop a subset of the pathophysiological features observed in humans such as robust glial and inflammatory responses, cell death or Tau dysfunction [13], [97]. One possible reason is that mouse models are usually based on the mutation of a single gene when AD in patients is associated with multiple gene variants – more than 50 loci have been already shown to promote the development of AD [98], [19]. Another possible reason lies in the inherent features of rodents versus humans.

Opportunities

- Conducting research on the underlying pathways leading to dementia in humans should allow the development of rodent models that better match the sequence of pathological and phenotypical events and might improve the translatability of research from rodents to humans (e.g. various mutations/comorbidities).

- Developing alternative models based on human cells, e.g. patient-derived induced pluripotent stem cells-based organoids, may facilitate the translation of pre-clinical research to humans.

6.3. Challenges related to the development and qualification of biomarkers

Current status and challenges

Biomarker acceptance by regulators, or biomarker qualification, facilitates the use of these biomarkers in a clinical trial setting for a defined context of use. Currently, biomarkers in AD qualified by the EMA are restricted to enrichment markers (see annex 8.1) and the last one dates back to 2012. The current lack of biomarkers, validated as per literature or qualified by regulatory agencies, can be explained by several factors:

- Current biomarker-based diagnostic tools (CSF-based and imaging) present major drawbacks: they are invasive and require a complex infrastructure. Although research is ongoing, detecting biomarkers in the peripheral fluids is often challenging due to their particularly low concentration.
- Clinical studies to validate biomarkers are often inadequately designed. For instance, biomarkers should be validated within a defined context of use in prospective studies rather than in observational studies, patients selection is inadequate (lack of stratification, bias introduced by volunteers participating in the trials).
- The conduction and analysis of biomarker-based tests varies across laboratories despite the use of similar commercially available assays. The source of variation can come from the pre-analytical conditions such as storage conditions, number of freeze-thaw cycles, in the conduction of the test, e.g. imaging parameters, and in the analysis criteria, e.g. cut off values [99]. A study conducted by the Alzheimer's Association Quality Control program between 2009 and 2013 showed a coefficient of variation between 20 and 30% for most assays, preventing the establishment of universal cutoffs [100], [101].
- Developers of biomarkers, especially in Academia, are not necessarily aware of the evidence expectation that regulators have for the different contexts of use.
- The long and expensive regulatory approval for the qualification of biomarkers discourage developers, in particular academic researchers, to validate their biomarkers [21], as shown by the small amount of qualification opinions published by EMA, the last one dating back to 2012 (see annex 8.1).
- Given the current lack of understanding of the pathophysiological mechanisms leading to AD and in absence of biomarkers that predict clinical outcomes, biomarkers cannot be accepted as surrogate endpoints in efficacy assessment.

Opportunities

- Once research has successfully determined the underlying disease pathways for dementias, there will be opportunities for new biomarkers.
- Recent developments have unraveled how diverse Tau spreading patterns in the brain of patients relate to specific clinical presentations [102], [103]. Advancing imaging techniques on Tau and other biomarkers will help to improve AD diagnosis and prognostic and to better select patients for clinical trials.
- Regulators should engage with academics partners who lead in these areas both in terms of explaining the technical requirements for validating biomarkers for regulatory use and in terms of facilitating formal interactions (including fee waivers for qualifications).

- Data sharing and analysis of large-scale data sets across neurodegenerative diseases should be encouraged to promote the identification of biomarkers. In addition, the generation and availability of biomedical information has exponentially increased (multi-omics data, electronic health records…), but the presentation of these data is heterogenous and interpretation complicated. Common databases for use across consortia/academic researchers and clinicians with a similar format should be created. Artificial intelligence (AI) further represents a unique opportunity to standardize and analyse these data and provide insight into the heterogeneity of neurodegenerative disorders and their associated biomarkers [104].
- As mentioned in section 4.2., liquid biopsies, in particular blood tests, are gaining significant interest due to their advantages (easily accessible, cost-effective, no complex facility nor training required). The development and use of ultrasensitive detection technologies should allow the validation of plasma biomarkers.
- The establishment of standard operating procedures for the collection and handling of samples prior to analyses, for the conduct of the tests and for the analysis should promote the reliability and reproducibility of the biological results. The creation of a certified reference material should also promote biomarker standardization. The development of fully automated methods that can be used in clinical laboratory practice and scaled up to large sample numbers could also help towards a harmonized approach. Certain fully-automated instruments have already demonstrated a reduced inter-laboratory coefficient of variation compared to classic tests [100]. Deep learning approaches are also being developed and applied for the automation of imaging data analysis. Such approaches should reduce variability in the analysis and interpretation of imaging biomarkers such as PET and MRI [37], [105].
- Recent advances in the field of AI and digital technologies/devices should allow the objective quantification of an increasing number of parameters, e.g. in cognition, behaviour or function [106]. For instance, efforts are being made to detect subtle early changes in olfaction, taste and speech that can predict AD or discriminate it from other dementias [12]. Besides allowing the objective detection of subtle changes, digital health technologies should enable a cost-effective, frequent and remote data sampling.

6.4. Challenges in clinical trials besides lack of biomarkers

Current status and challenges

Clinical trials for Alzheimer's disease are associated with a variety of challenges. First, the small populations included in clinical trials (e.g. patients with ApoE4 mutation) are not representative of the heterogeneity of the AD population.

Second, meeting a clinical endpoint using the current psychometric tests is difficult. Efficacy assessment using existing cognitive and/or functional clinical outcomes in pre-clinical AD and prodromal AD/MCI is challenging, demonstrating ceiling effects and only subtle changes over the course of the clinical trials [18], [90], [102]. As a result, the duration of a trial might need to be very long before a treatment achieves a noticeable effect on a clinical endpoint. In 2022 for instance, the average treatment duration for Phase 3 prevention trials was of 159 weeks [23]. The generation and evaluation of clinical outcome measurement tools that combine clinical meaningfulness and sensitivity to changes in the early stages of AD require specific expertise.

Third, uncertainties on how to handle long trials in a changing landscape remain. AD is slowly progressive in general and development of clinical signs and symptoms take years depending on the stage of AD evaluated. Duration of the studies are poorly adapted to that even with the more sensitive cognitive and/or functional clinical outcomes. Performing long term studies is a challenge, for instance in terms of occurrence and

impact of intercurrent events, including patients starting novel medicines if they are approved during a trial. However, trials for AD will likely still need to be of long duration, in particular as the research goes into earlier stages and surrogate biomarkers are still not available.

Besides, there is no consensus on how clinical trials targeting a presymptomatic population - desirable ethically as to maximise time spent without symptoms and perhaps biologically as the downstream cascades might be difficult to interrupt - should be conducted (i.e. on what population and on which endpoints).

Finally, the integration of patient- and caregiver-reported outcomes is lacking. Besides assessments tools reporting core disease outcomes on cognition and daily function as reported by clinicians, patient-, caregiver- and observer-reported outcomes should be integrated in the clinical assessment. While patient-reported outcomes might have a limited value when used in AD dementia, they are particularly important in the preclinical and prodromal AD stages. More studies are needed to investigate how well the clinical outcome assessment tools currently used capture the needs, preferences, and priorities of individuals, to develop such measures and validate their utility [107], [108].

Opportunities

- Recent advances in the field on real world data, AI and digital technologies and devices in general will likely allow the detection of subtle changes in cognition, function (e.g. spoken language, eye movements, spatial navigation performance) and other changes (e.g. sleep) and could have the potential to predict which subjects are likely to progress to AD [109], [110]. Key advantages include sensitivity of these measurements, objectivity, timely detection of changes (real-time measurement or at least large amount of data sampling) and remote control and assessment.
- The further development of multidomain tests and composite scores combining cognitive and functional dimensions should ease the detection of subtle clinical changes as they are less influenced by factors such as the educational level or lifestyle [111], [112].
- Including patient- and observer-reported outcomes (e.g. maintaining relationships and social connections, enjoying life, preserving a sense of identity, conversational skills), health and economic outcomes (e.g. use of healthcare resources, work status) and neuropsychiatric symptoms in addition to the core disease outcomes related to cognition and function should help assessing the clinical benefit of compounds [107].
- Research in both the choice of strategies and on estimators within the estimands framework is needed.

6.5. Preparedness of health care systems

Current status and challenges

General practitioners are in the front line to screen and identify higher risk patients. However, most general practitioners acknowledge not being trained for identifying early symptoms and diagnostic tools required to make an initial diagnosis are lacking. In addition, European healthcare systems currently lack MRI capacity and the capacity of expert clinicians trained to detect, diagnose and treat AD patients [6], [113]. In 2018, modelling the healthcare capacity of 6 European countries predicted the peak wait times to range from five months for treatment in Germany to 19 months for evaluation in France. This time would be sufficient for about 1 million patients with mild cognitive impairment to see their disease progress to AD while on waiting list between 2020 and 2044 [114]. Besides, most European countries will not have the capacity to provide infusions to all AD patients in a timely manner when a DMT requiring near-monthly visits for its administration will become available. Finally, current diagnostic tools require a training, cannot be routinely performed outside specialized centres and their reimbursement varies across Europe [6].

Opportunities

- Developing screening and diagnosis guidelines and updating them to match ongoing research developments should be promoted.
- Training geriatric health care professionals - and health care professional in general - to cognitive assessment should facilitate a timely evaluation of patients who self-report a concern about cognition, behaviour or functioning; or for whom relatives/clinicians identify/suspect such concerns [6], [115].
- Primary care providers should be incentivized to refer most at-risk patients to dementia specialists for further clinical evaluation.
- Specialists capacity and facilities (e.g. MRI capacity) should be built.
- Targeted screening of populations at risk to ensure early detection and access to treatment should be implemented if ethics permits (see part 6.6).
- Digital tools should be leveraged to assess and monitor cognition and function proactively.
- Infusion centres should be built as extensions to existing facilities and home infusions used when possible.

6.6. Ethical considerations

Current status and challenges

Although information on biomarkers enhances diagnosis, a substantial portion of elderly with abnormal biomarkers for AD never develop dementia [93], [94]. If testing is offered, its potential consequences need to be discussed. The current lack of predictive values of biomarkers, the absence of DMT and the anxiety induced by AD diagnostic hold back professionals from testing. Some physicians even argue that testing and informing patients can be in conflict with the physician's oath of *primum non nocere* (first, do no harm). On the other side, the right of patients to know, the possibility to change lifestyle practices, to seek for additional support from health care professionals, to plan the future in terms of private, professional, financial and legal matters and to allow individuals to participate in prevention trials are arguments in favor of biomarker disclosure [116].

The involvement of patients in the definition of the benefit to risk ratio of a new medicine is crucial. However, the consent of patients suffering from dementia poses ethical questions. This question is particularly relevant in the context of AD, where the risk of adverse events amyloid-related imaging abnormalities (ARIA) is reported [117], [118], [119].

Opportunities

- Conducting research on the potential psychological harm and benefit triggered by the disclosure of positive biomarkers in a clinical and research settings should help the establishment of an ethical framework [120].
- Providing guidance on when (e.g. which biomarkers results can be communicated, in a research or clinical setting) and how (risk communication) to disclose biomarker results to research participants is needed. The fields of oncology and genetic testing constitutes a good example to follow [116], [121].

7. Recommendations

7.1. Encouraging funding

- Promoting funding dedicated to the research on the pathophysiology of AD and other age-related neurodegenerative dementias and on biomarkers.
- Encouraging the creation of a research data repository gathering studies, datasets and biosamples from inherited AD patients.
- Encouraging comprehensive data sharing and collaboration across dementias and more generally across age-related neurodegenerative diseases.

7.2. Building expertise within the regulatory network or access to such knowledge / expertise via external experts

- Establishing and expanding capacity for psychometricians in the European Medicines Regulatory Network: complex neuropsychological tests and any other kinds of outcome measurement tools need to be assessed for their psychometric properties.
- Continuing capacity building for expertise on the regulatory side for AD developments and applications implementing digital tools, remote diagnostics or AI in clinical research.
- Engaging with and involving patient organizations in the evaluation of AD therapeutics.

7.3. Promoting the development of new methodologies, including biomarkers for patient selection and efficacy endpoints for trials of regulatory interest

- Establishing guidelines for biomarker validation (i.e. scientific requirements for use in non-regulatory context and validated by the scientific community) and qualification (i.e. for use in the context of regulatory dossiers and accepted by regulatory agencies) in order to build a consistent methodological framework.
- Besides guidelines, training researchers (in particular academia and SMEs) and increasing awareness on the need to follow regulatory requirements for the acceptance of a biomarker in the context of a clinical trial (see part challenges part 6.3 on the lack of regulatory knowledge).
- Setting-up and fostering the development of research guidelines on biomarker processing, analysis and interpretation to promote standardization of the results.
- Continuing to engage on and advance the methodology of clinical trials and statistical analyses for trials of long duration and with high incidence of intercurrent events.
- Setting-up recommendations or guidelines for the use of biomarkers in clinical research and clinical practice according to their context of use for researchers and healthcare professionals.
- Establishing guidance documents on traceability, quality and integrity of data obtained from wearables as well as on the application of the Findable, Accessible, Interoperable, and Reusable (FAIR) principles; collaborating and interacting with the research community on the specific use of such tools and their output data for answering AD research questions.
- Setting up guidance documents/standards for the use of an open source platform for non-clinical data collection and data exchange.
- Updating the regulatory guidance in response to (i) the availability of DMTs and (ii) the need of characterising long-term efficacy and safety (including stopping rules) of DMTs.

7.4. Providing guidance on transdiagnostic and/or symptom specific indications

- In consideration of the CNS WP workplan ("Prepare the expert network for both the challenges and opportunities in situations when disease definitions are uncertain and subject to change"), seeking a common understanding of the regulatory challenges and opportunities associated with the adoption of a transdiagnostic approach, e.g. by means of expanding connections and links to academic and clinical experts, data sharing initiatives across consortia and implementation of registries.

7.5. Updating disease definition and provide guidance on clinical development of therapies at the pre-symptomatic stage

- Engaging on the concept of pre-symptomatic stage of neurodegenerative disease and on the definition of "Alzheimer's disease" in particular, which can be updated with new scientific knowledge and society standards.
- In line with the CNS WP workplan ("Develop consistent principles for feasible, efficient and robust data generation in the asymptomatic phase of neurodegenerative disorders. With an ageing population in the EU, and the observed progress in scientific research on the topic that could potentially allow prevention of symptomatic diseases, a consistent approach to studying the asymptomatic phases of neurodegenerative disorders is highly needed"), engaging discussions on how to investigate pre-clinical, asymptomatic AD in order to allow the development of a preventive approach.

8. Annexes

8.1. List of qualification opinion published by EMA to support the use of biomarkers

1. Qualification opinion of novel methodologies in the predementia stage of Alzheimer's disease: cerebro - spinal fluid related biomarkers for drugs affecting amyloid burden. EMA/CHMP/SAWP/102001/2011	
Link to webpage	Qualification opinion of novel methodologies in the predementia stage of Alzheimer's disease: cerebro - spinal fluid related biomarkers for drugs affecting amyloid burden (europa.eu)
Scope	"The present opinion addresses the question as to whether the use of two cerebral spinal fluid (CSF) related biomarkers (Aβ1-42 and total tau 1) are qualified in selecting (i.e. to categorize) subjects for trials in early Alzheimer's Disease (AD) as having a high probability of being in the prodromal stage of the disease."
Opinion	"The CSF biomarker signature based on a low Aβ1-42 and a high-tau qualifies to enrich clinical trial populations"
Year of adoption	2011
2. Qualification opinion of low hippocampal volume (atrophy) by MRI for use in clinical trials for regulatory purpose - in pre-dementia stage of Alzheimer's disease. EMA/CHMP/SAWP/809208/2011	
Link to webpage	Qualification opinion of low hippocampal volume (atrophy) by MRI for use in clinical trials for regulatory purpose - in pre-dementia stage of Alzheimer's disease (europa.eu)
Scope	"The present opinion addresses the question as to whether the use of baseline measurement of low hippocampal volume (atrophy) by MRI is qualified in selecting (i.e. to categorize) subjects for trials in early Alzheimer's Disease (AD) as having a high probability of being in the prodromal stage of the disease as defined by the Dubois Criteria (2007)"
Opinion	"Low hippocampal volume, as measured by MRI and considered as a dichotomized variable (low volume or not), appears to help enriching recruitment into clinical trials aimed at studying drugs potentially slowing the progress/conversion to AD dementia of the included subjects."
Year of adoption	2011
3. Qualification opinion of Alzheimer's disease novel methodologies/biomarkers for PET amyloid imaging (positive/negative) as a biomarker for enrichment, for use in regulatory clinical trials in predementia Alzheimer's disease	
Link to webpage	Qualification opinion of Alzheimer's disease novel methodologies/biomarkers for PET amyloid imaging (positive/negative) as a biomarker for enrichment, for use in regulatory clinical trials in predementia Alzheimer's disease (europa.eu) EMA/CHMP/SAWP/892998/2011
Scope	"Qualification opinion of Alzheimer's disease novel methodologies/biomarkers for PET amyloid imaging (positive/negative) as a biomarker for enrichment for use in predementia AD clinical trials"

Opinion	"Amyloid related positive/negative PET signal qualifies to identify patients with clinical diagnosis of predementia AD who are at increased risk to have an underlying AD neuropathology, for the purposes of enriching a clinical trial population"
Year of adoption	2012
4. Qualification opinion of Alzheimer's disease novel methodologies/biomarkers for the use of CSF AB 1-42 and t-tau and/or PET-amyloid imaging (positive/ negative) as biomarkers for enrichment, for use in regulatory clinical trials in mild and moderate Alzheimer's disease	
Link to webpage	Qualification opinion of Alzheimer's disease novel methodologies/biomarkers for the use of CSF AB 1-42 and t-tau and/or PET-amyloid imaging (positive/ negative) as biomarkers for enrichment, for use in regulatory clinical trials in mild and moderate Alzheimer's disease (europa.eu)
Scope	Qualification of Alzheimer's Disease Novel Methodologies/biomarkers for the use of CSF AB 1-42 and t-tau and/or PET-amyloid imaging (positive/ negative) as biomarkers for enrichment, for use in Regulatory Clinical Trials in Mild and Moderate of Alzheimer's disease.
Opinion	"CSF biomarker signature based on a low Aβ1-42 and a high T-tau qualifies to identify patients with clinical diagnosis of mild to moderate AD who are at increased risk to have an underlying AD neuropathology, for the purposes of enriching a clinical trial population." "Amyloid related positive/negative PET signal qualifies to identify patients with clinical diagnosis of mild to moderate AD who are at increased risk to have an underlying AD neuropathology, for the purposes of enriching a clinical trial population."

8.2. List of EU grants for neurodegenerative research since 2014

Topic ID/Project	Name	Topic	Budget (EUR)	Opening Date	Deadline Date(s)
IHI-PROMINENT project	A digital platform able to give personalized, timely and accurate information about the current disease state, prognosis, and potential benefits and risks with novel therapies.	The PROMINENT digital platform will be built upon prediction models trained on large, representative datasets, that use a wide range of factors including demographics, clinical history, cognitive tests, diagnostic imaging, fluid biomarkers and genetics to produce predictions of the correct diagnosis, future course of disease and care needs which are then combined with data on performance and cost of diagnostic tests, to generate optimized diagnostic algorithms.	11 069 750 (6 069 750 IHI + 5 000 000 contributing partners)	1 May 2023	20 April 2028
HORIZON-HLTH-2024-DISEASE-03-13-two-stage	Validation of fluid-derived biomarkers for the prediction and prevention	Validate biomarkers that can reliably confirm early stages of the human brain disorder and guide treatment/ intervention selection.	25 000 000	26 April 2023	19 September 2023 11 April 2024

Topic ID/Project	Name	Topic	Budget (EUR)	Opening Date	Deadline Date(s)
	of brain disorders.				
EU4H-2023-PJ-04	Call for proposals on prevention of NCDs around dementia and other neurological disorders	Implementation of projects involving civil society organisations to support implementing comprehensive public health policies, the development and transfer of best practices, public health guidelines, the preparation and roll-out of innovative approaches and supporting patient pathway, and launching of training, health awareness and health literacy projects	1 000 000	15 June 2023	17 October 2023
HORIZON-HLTH-2023-STAYHLTH-01-01	The Silver Deal - Person-centred health and care in European regions	Citizens and patients will get effective, preventive, integrated, coordinated, evidence-based and people-centred high-quality health and care services to identify and tackle or prevent multi-morbidities, frailty, biologically or mentally reduced capacities, (sensory) impairments, dementia and/or neurodegeneration, fostering mental and physical health, wellbeing, and quality of life.	40 000 000	12 January 2023	13 April 2023
HORIZON-HLTH-2023-DISEASE-03-06	Towards structuring brain health research in Europe	Tackling non-communicable diseases and reducing disease burden	1 000 000	12 January 2023	13 April 2023
IMI2 - Call 23	European Platform for Neurodegenerative Diseases (EPND)	The aim of EPND is to establish a collaborative platform via a European node on the AD Workbench of the Alzheimer's Disease Data Initiative (ADDI) that would link up existing European research infrastructures and so speed up the discovery of new biomarkers for neurodegenerative diseases.	19 005 502 (IMI Funding 9 680 000 EFPIA in kind 9 325 500 Other 2)	01 November 2021	31 October 2026
IMI2 - Call 22	Psychiatric Ratings using Intermediate Stratified Markers 2 (PRISM 2)	The goal of the PRISM 2 project is to build on the achievements of the original PRISM project. Specifically, it aims to validate PRISM's findings on social withdrawal in schizophrenia and Alzheimer's disease and investigate whether they also apply to major depressive disorder. The work of this follow-up project should ensure that these validated findings will result in more accurate	7 894 554 (IMI Funding 3 980 906 EFPIA in kind 2 825 181 Associated Partners	01 June 2021	31 May 2023

Topic ID/Project	Name	Topic	Budget (EUR)	Opening Date	Deadline Date(s)
		diagnoses and treatments for people with Alzheimer's disease, schizophrenia and major depressive disorder.	1 088 466)		
IMI2-2020-23-03	A platform for accelerating biomarker discovery and validation to support therapeutics development for neurodegenerative diseases	Create a set of agreed principles to enable sharing and access to data and samples of neurodegenerative diseases and establish a self-sufficient network that can house high quality data and samples, which could have federated and centralised elements.	95 150 000 (unspecified, divided between 6 projects)	23 June 2020	29 September 2020 17 March 2021
IMI2 - Call 13	NEURONET, efficiently networking European neurodegeneration research	The NEURONET platform aims to be a key enabler and mediator across the growing neurodegenerative disorders (ND) portfolio, assisting in identifying gaps, multiplying impacts, enhancing visibility and ensuring coordination with related initiatives in Europe and worldwide.	2 353 125 (IMI Funding 1 199 125 EFPIA in kind 1 010 000 Associated Partners 144 000)	01 March 2019	31 September 2022
IMI2 - Call 12	Investigating mechanisms and models predictive of accessibility of therapeutics (IM2PACT) into the brain.	The goal of IM2PACT is to advance our understanding of the BBB to facilitate the development of more effective treatments for a range of neurological and metabolic disorders. Specifically, the project aims to develop better models of the blood-brain barrier (BBB) so that researchers can study it more easily; investigate the biology of the BBB in both health and disease, and the transport routes across it; and to develop innovative systems capable of delivering medicines to the brain, especially concerning the context of neurodegenerative and metabolism-related diseases treatment.	17 410 136 (IMI Funding 9 000 000 EFPIA in kind 8 410 136)	01 January 2019	31 December 2024
IMI2-2018-15-06	Digital endpoints in neurodegenerative and immune-mediated diseases	develop a technology platform to collect and analyse sensor/generated datasets, principally high resolution passively and actively collected digital measurements, i.e. actigraphy, socialisation parameters and momentary self-reported assessments of	386 722 862 (unspecified, divided between 8 projects)	18 July 2018	24 October 2018 15 May 2019

Topic ID/Project	Name	Topic	Budget (EUR)	Opening Date	Deadline Date(s)
		Subtle impairments in accomplishing daily activities, the first signs of a neurodegenerative disorder. This is done to Identify the ADLs that first or more consistently are affected by the disorders and tracing their progression over time.			
IMI2-2017-13-05	Support and coordination action for the projects of the Neurodegeneration area of the Innovative Medicines Initiative	Create a platform to enable the mapping of partnerships and collaborative efforts that have supported over the past years research in Alzheimer's disease to capture their contributions and identify the remaining gaps and develop metrics and benchmarks to measure value, including socio-economic impact	223 050 000 (unspecified, divided between 15 projects)	30 November 2017	28 February 2018 06 September 2018
IMI2-2017-13-06	A sustainable European induced pluripotent stem cell platform	Establish a fully self-sustainable European human iPSC banking facility by building on and incorporating existing cell lines, knowledge and infrastructure established within former European-wide initiatives (like EBiSC). The bank must be able to handle and deliver a minimum of approximately 500 quality-controlled, disease-relevant, research-grade Induced pluripotent stem cells lines	223 050 000 (unspecified, divided between 15 projects)	30 November 2017	28 February 2018 06 September 2018
IMI2-2017-13-04	Mitochondrial Dysfunction in Neurodegeneration	Develop an unprecedented appreciation of mitochondrial function in an in vivo model of neurodegenerative disease	223 050 000 (unspecified, divided between 15 projects)	30 November 2017	28 February 2018 06 September 2018
IMI2-2017-12-01	Development and validation of technology enabled quantitative and sensitive measures of functional decline in people with early-stage Alzheimer's Disease (RADAR-AD)	Identify functional domains or markers that are specific and sensitive to early stages of Alzheimer's progression and most predictive of deleterious long-term outcomes such as loss of independence and nursing home entry using a digital platform that would draw on smartphone, wearable and home-based digital technologies.	7 659 120 (IMI Funding 4 999 757 EFPIA in kind 2 331 652 Associated Partners 223 132 Other 104 579, Part of a grant of	19 July 2017	24 October 2017 16 May 2018

Topic ID/Project	Name	Topic	Budget (EUR)	Opening Date	Deadline Date(s)
			126 439 000 divided between 7 projects)		
IMI2-2017-12-06	Discovery and characterisation of blood-brain barrier targets and transport mechanisms for brain delivery of therapeutics to treat neurodegenerative & metabolic diseases	Better understand the role and alterations of the Blood Brain Barrier (BBB) and transport mechanisms in neurodegenerative diseases by establishing BBB models relevant for healthy and disease conditions for evaluation of disease-modifying agents (human in vitro cell based, in particular iPSC or progenitor-derived cells, and in vivo)	126 439 000 (unspecified, divided between 7 projects)	19 July 2017	24 October 2017 16 May 2018
SC1-HCO-04-2018	ERA-NET to support the Joint Programming in Neurodegenerative Diseases strategic plan (JPND)	Building on earlier successes of the JPND Research Strategy in scaling-up and establishing synergies with Horizon and continue previous efforts to consolidate defragmentation, better coordination and alignment amongst the countries participating in the JPND.	5 000 000	07 November 2017	18 April 2018
SC1-BHC-23-2018	Novel patient-centred approaches for survivorship, palliation and/or end-of-life care	Development of pharmacological and/or non-pharmacological interventions to either relieve symptoms and suffering caused by life-threatening non-communicable diseases (including disabilities), or serious late and long-term side effects of disease treatments in patients and survivors, or symptoms that occur at the end of life.	44 000 000	07 November 2017	18 April 2018
IMI2 - Call 9	European Quality in Preclinical Data (EQIPD)	The EQUIPD project aims to assess the urgent need for simple, sustainable solutions to improve data quality by delivering simple recommendations to facilitate data quality without impacting innovation and developing an EQIPD quality management system by analysing the variables in study design and data analysis that influence outcomes in academia and industry projects.	9 360 692 (IMI Funding 4 495 523 EFPIA in kind 4 609 347 Other 255 822)	01 October 2017	30 September 2021

Topic ID/Project	Name	Topic	Budget (EUR)	Opening Date	Deadline Date(s)
IMI2 - Call 7	Inhibiting misfolded protein propagation in neurodegenerative diseases (IMPRiND)	The IMPRiND project aims to understand how aggregated proteins, misfolded proteins which clump together leading to a progressive spreading of the brain cells degeneration, are handled once inside brain cells and how they are moved from cell to cell.	11 388 398 (IMI Funding 4 684 998 EFPIA in kind 6 390 900 Other 312 500)	01 March 2017	28 February 2022
IMI2 - Call 7	Big Data for Better Outcomes (BD4BO/ DO->IT)	BD4BO was built around four different IMI projects, each centred on a particular disease. DO->IT was not a typical IMI research project but rather a coordinating 'entity' that was intended to help with two things: firstly, to coordinate the different activities of the four data-driven IMI projects that make up the BD4BO programme, raise awareness of their existence, and communicate to the scientific community their findings, results and educational materials. Secondly, DO->IT's mission was to sort out thorny issues relating to informed consent forms, the documents that patients fill in to signal their agreement about who is allowed to use their data.	7 191 755 (IMI Funding 3 549 833 EFPIA in kind 3 604 817 Other 37 105)	01 February 2017	31 January 2019
IMI2 - Call 6	Real world outcomes across the AD spectrum for better care: multi-modal data access platform (ROADMAP)	The ROADMAP project developed his Alzheimer's "Data Cube", an online, three-dimensional 'heat map' that uses information from 65 sources between electronic health records, clinical trials, and cohorts, to allow users to visualise how different data sources capture different Alzheimer's disease outcomes at different disease stages, what data sources are available, and where there are gaps. This kind of tools have been proven to be very useful for the design, planning and validation of the models and strategies used to guide future recommendations to enhance AD research.	8 210 381 (IMI Funding 3 998 250 EFPIA in kind 4 210 843 Other 1 28)	01 November 2016	31 October 2018

Topic ID/Project	Name	Topic	Budget (EUR)	Opening Date	Deadline Date(s)
IMI2 - Call 5	PHAGO Project	The PHAGO project aims to develop tools and methods to study the workings of two genes that appear to be involved in this immune response to Alzheimer's disease, TREM2 and CD33. By doing so the project aims to pave the way for the development of novel drugs that could tackle Alzheimer's disease by interacting with these genes.	18 221 231 (IMI Funding 8 838 000 EFPIA in kind 9 445 395 Other 10 080)	01 November 2016	30 April 2022
IMI2 - Call 5	Amyloid imaging to prevent Alzheimer's disease (AMYPAD)	The goal of AMYPAD is to determine the clinical added value of PET imaging in diagnosis and patient monitoring. This will be accomplished by developing data to establish its usefulness in clinical trials, data gathered by carry out beta amyloid PET imaging on an unprecedented number of people who are suspected to be in the early stages of Alzheimer's disease.	27 329 288 (IMI Funding 11 999 886 EFPIA in kind 12 233 950 Other 3 095 452)	01 October 2016	30 September 2022
IMI2 - Call 5	Alzheimer's disease apolipoprotein pathology for treatment elucidation and development (ADAPTED)	The ADAPTED project aims to boost the development of new medicines by investigating an under researched area of AD research, the APOE gene, a well-known risk factor for developing the disease who's precise impact on AD risk is yet to be precisely measured.	6 796 740 (IMI Funding 3 510 000 EFPIA in kind 3 286 740)	01 October 2016	30 September 2020
IMI2 - Call 5	Models of patient engagement for Alzheimer's disease (MOPEAD)	The MOPEAD project set out to establish what could be done about identifying people who could participate in the AD clinical trials that focus on the earlier stages of the disease more accurately and what stands in their way of coming forward. They tested four different methods of screening for potential cases and engaging those suspected of having some degree of cognitive impairment across 5 European countries in order to establish the best ways to intervene in varied situations and groups.	4 581 968 (IMI Funding 2 043 000 EFPIA in kind 1 967 251 Other 571 717)	01 October 2016	31 December 2019

Topic ID/Project	Name	Topic	Budget (EUR)	Opening Date	Deadline Date(s)
IMI2 - Call 3	Psychiatric Ratings using Intermediate Stratified Markers (PRISM)	The PRISM project wanted to get to the root biological causes of behavioural symptoms by carrying out a range of tests on patients with neuropsychiatric disorders in a bid to determine which biological parameters can be matched with specific clinical symptoms like social dysfunction. They identified quantitative biological parameters in the hope that yhey will ultimately provide leads for new drugs, which are sorely lacking for these diseases.	16 195 875 (IMI Funding 8 080 000 EFPIA in kind 8 115 875)	01 Aprile 2016	30 Settembre 2019
IMI2-2015-07-02	IDENTIFICATION OF DRUGGABLE TARGETS MODULATING MISFOLDED PROTEINS IN ALZHEIMER'S AND PARKINSON'S DISEASES	Setting up both in vitro and in vivo model systems for spreading and seeding processes to better understand the molecular mechanisms involved in the spreading, uptake, seeding, aggregation, of tau and alpha-synuclein and their impact on cell homeostasis, release, and toxicity.	93 604 000 (unspecified, divided between 7 projects)	18 December 2015	17 March 2016 06 September 2016
IMI2-2015-06-03	Real World Outcomes Across the AD Spectrum (ROADS) to Better Care	Define a set of measurable patient-relevant real-world outcomes, characterize the spectrum of AD and provide recommendations of different approaches to model disease progression to enable better treatment selection and improved health care value for AD patient.	93 000 000 (unspecified, divided between 4 projects)	06 October 2015	12 January 2016 14 June 2016
IMI2-2015-05-04	Understanding the role of amyloid imaging biomarkers in the current and future diagnosis and management of patients across the spectrum of cognitive impairment (from pre-dementia to dementia).	Understand the utility of β-amyloid imaging in the context of other biomarkers and diagnostic tests in current clinical practise in AD	12 000 000	09 July 2015	13 October 2015 15 March 2016
IMI2-2015-05-06	From ApoE biology to validated Alzheimer's	Identify critical mechanism(s) by which Apolipoprotein E ε4 (ApoE4) leads to the development of AD.	2 640 000	09 July 2015	13 October 2015

Topic ID/Project	Name	Topic	Budget (EUR)	Opening Date	Deadline Date(s)
	disease targets				
IMI2-2015-05-05	Evolving models of patient engagement and access for earlier identification of Alzheimer's disease: Phased expansion study	Establish multiple key regional project sites (across Europe to identify and test models of efficient earlier identification of mild AD dementia and prodromal AD patients, and awareness of AD risk; and assess key tools, mechanisms and processes for community engagement and patient identification and resource utilization in various communities.	2 043 000	09 July 2015	13 October 2015
IMI1 - Call 11	European prevention of Alzheimer's dementia consortium (EPAD)	The EPAD project is pioneering a novel, more flexible approach to clinical trials of drugs designed to prevent Alzheimer's dementia that uses an 'adaptive' trial design to deliver better results faster and at lower cost.	58 986 698 (IMI Funding 25 880 000 EFPIA in kind 26 784 499 Other 6 322 199)	01 January 2015	31 October 2020
FETOPEN-RIA-2014-2015	FET-Open research projects	Support a large set of early stage, high risk visionary science and technology collaborative research projects.	154 000 000	11 December 2013	30 September 2014 31 March 2015 30 September 2015
NMP-12-2015	Biomaterials for treatment and prevention of Alzheimer's disease	Develop new multifunctional biomaterials, as part of eventual Medical Devices and Advanced Therapies, which aim to create, optimise, enhance, substitute or support preventive and therapeutic interventions in Alzheimer's disease.	148 370 000 (unspecified, divided between 9 projects)	22 October 2014	26 March 2015 08 September 2015
PHC-22-2015	Promoting mental wellbeing in the ageing population	multi-disciplinary research to improve the understanding, prevention, early diagnosis, and treatment of mental conditions and disorders of older people.	306 000 000 (unspecified, divided between 9 projects)	30 July 2014	14 October 2014 21 April 2015
HCO-17-2015	Towards sustainability and globalisation of the Joint Programmin	Development and extension of the JPND capacities. Explore possible scenarios for long-term sustainability by Member States and create political awareness to prepare their	29 000 000 (unspecified, divided between	30 July 2014	24 February 2015

Topic ID/Project	Name	Topic	Budget (EUR)	Opening Date	Deadline Date(s)
	g Initiative on Neurodegenerative Diseases	implementation, extend the capacities of the JPND globally and to the Members States which are not yet participating and develop and implement current and new strategies for further coordination of national and JPND research agendas.	4 projects)		
IMI1 - Call 8	AETIONOMY	AETIONOMY project developed an innovative way to classify neurodegenerative diseases Alzheimer's (AD) and Parkinson's (PD) based on the mechanism i.e. cause(s) of disease. The project developed a prototype for a taxonomy that will change how the drivers of these diseases are analysed.	17 812 216 (IMI Funding 7 993 234 EFPIA in kind 8 021 460 Other 1 797 522)	01 January 2014	31 December 2018
IMI1 - Call 8	European Bank for induced pluripotent Stem Cells (EBiSC)	The European Bank for Induced Pluripotent Stem Cells (EBiSC) was established to provide researchers across academia and the pharmaceutical industry with disease-relevant, quality-controlled, research-grade iPSC lines, data and cell services, and to promote the wider use of iPSCs in researches covering neurodegenerative diseases, diabetes, eye and heart diseases and muscular dystrophies.	34 327 858 (IMI Funding 21 840 380 EFPIA in kind 7 167 072 Other 5 320 406)	01 January 2014	31 December 2017
HCO-07-2014	ERA-NET: Establishing synergies between the Joint Programming on Neurodegenerative Diseases Research and Horizon 2020.	Implementing a transnational call with EU co-funding resulting in grants to third parties, with a view to scale-up the implementation of the JPND Research Strategy.	36 000 000 (unspecified, divided between 10 projects)	11 December 2013	15 April 2014
IMI1 - Call 4	European Medical Information Framework (EMIF)	The EMIF project created an IT tool that allows researchers to browse a 'catalogue' of data sources, and use a secure remote environment in which to access, analyse, visualise and ultimately, reuse, the datasets while respecting patient privacy.	55 784 311 (IMI Funding 24 356 096 EFPIA in kind 24 354 503	01 January 2013	30 June 2018

Topic ID/Project	Name	Topic	Budget (EUR)	Opening Date	Deadline Date(s)
			Other 7 073 712)		

9. Bibliography

[1] Heads of Medicines Agencies, 'EU-INNOVATION NETWORK (EU-IN) Introduction and Overview'. Accessed: Aug. 17, 2023. [Online]. Available: https://www.hma.eu/about-hma/working-groups/eu-innovation-network-eu-in.html

[2] European Medicines Agency, 'EMA Regulatory Science to 2025', p. 79, Mar. 2020.

[3] Heads of Medicine Agencies and European Medicines Agency, 'European medicines agencies network strategy to 2025: Protecting public health at a time of rapid change', 2020.

[4] E. Nichols *et al.*, 'Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019', *The Lancet Public Health*, vol. 7, no. 2, pp. e105–e125, Feb. 2022, doi: 10.1016/S2468-2667(21)00249-8.

[5] World Health Organization, 'Dementia: key facts'. [Online]. Available: https://www.who.int/news-room/fact-sheets/detail/dementia#:~:text=Key%20facts,nearly%2010%20million%20new%20cases.

[6] European Federation of Pharmaceutical Industries and Associations, 'Alzheimer's Disease Health System Readiness – The Time to Act is Now', Sep. 14, 2020. [Online]. Available: https://www.efpia.eu/media/554825/efpia-ad-platform-health-system-readiness.pdf

[7] World Health Organization, 'Global action plan on the public health response to dementia 2017 - 2025', 2017.

[8] Alzheimer's disease facts and figures, '2018 Alzheimer's disease facts and figures', Mar. 2018, [Online]. Available: https://alz-journals.onlinelibrary.wiley.com/doi/epdf/10.1016/j.jalz.2018.02.001

[9] Alzheimer's Association, '2020 Alzheimer's Disease Facts and Figures', 2020, [Online]. Available: https://www.alz.org/media/documents/alzheimers-facts-and-figures_1.pdf

[10] B. Dubois *et al.*, 'Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS–ADRDA criteria', *The Lancet Neurology*, vol. 6, no. 8, pp. 734–746, Aug. 2007, doi: 10.1016/S1474-4422(07)70178-3.

[11] M. S. Albert *et al.*, 'The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging - Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease', *Alzheimer's & Dementia*, vol. 7, no. 3, pp. 270–279, May 2011, doi: 10.1016/j.jalz.2011.03.008.

[12] G. M. McKhann *et al.*, 'The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease', *Alzheimers Dement*, vol. 7, no. 3, pp. 263–269, May 2011, doi: 10.1016/j.jalz.2011.03.005.

[13] L. K. Wareham *et al.*, 'Solving neurodegeneration: common mechanisms and strategies for new treatments', *Mol Neurodegeneration*, vol. 17, no. 1, p. 23, Dec. 2022, doi: 10.1186/s13024-022-00524-0.

[14] J. Hort *et al.*, 'EFNS guidelines for the diagnosis and management of Alzheimer's disease', vol. 17, no. 10, pp. 1225–1313, Oct. 2010, doi: 10.1111/j.1468-1331.2010.03040.x.

[15] European Brain Council's, 'Rethinking Alzheimer's disease detection and diagnosis', Mar. 2023, [Online]. Available: https://www.braincouncil.eu/wp-content/uploads/2023/04/RETHINK-AlzheimerDisease-Report_DEF3_HD_rvb_03042023.pdf

[16] G. McKhann, D. Drachman, M. Folstein, R. Katzman, D. Price, and E. M. Stadlan, 'Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group* under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease', *Neurology*, vol. 34, no. 7, pp. 939–939, Jul. 1984, doi: 10.1212/WNL.34.7.939.

[17] 'Consensus Recommendations for the Postmortem Diagnosis of Alzheimer's Disease', *Neurobiology of Aging*, vol. 18, no. 4, pp. S1–S2, Jul. 1997, doi: 10.1016/S0197-4580(97)00057-2.

[18] European Medicines Agency, 'Guideline on the clinical investigation of medicines for the treatment of Alzheimer's disease (CPMP/EWP/553/95 Rev.2)', Feb. 28, 2018. [Online]. Available: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicines-treatment-alzheimers-disease-revision-2_en.pdf

[19] C. R. Jack *et al.*, 'NIA - AA Research Framework: Toward a biological definition of Alzheimer's disease', *Alzheimer's & Dementia*, vol. 14, no. 4, pp. 535–562, Apr. 2018, doi: 10.1016/j.jalz.2018.02.018.

[20] B. Dubois *et al.*, 'Clinical diagnosis of Alzheimer's disease: recommendations of the International Working Group', *Lancet Neurol*, vol. 20, no. 6, pp. 484–496, Jun. 2021, doi: 10.1016/S1474-4422(21)00066-1.

[21] Alzheimer's Association, 'Revised Criteria for Diagnosis and Staging of Alzheimer's Disease: Alzheimer's Association Workgroup'. Accessed: Apr. 01, 2024. [Online]. Available: https://aaic.alz.org/diagnostic-criteria.asp

[22] Alzheimer's Aossication Workgroup, 'Draft Revised Criteria for Diagnosis and Staging of Alzheimer's Disease: Alzheimer's Association Workgroup', Oct. 25, 2023. Accessed: Apr. 01, 2024. [Online]. Available: https://alz.org/media/Documents/scientific-conferences/Clinical-Criteria-for-Staging-and-Diagnosis-for-Public-Comment-Draft-

2.pdf?_gl=1*14joo7h*_ga*MTgwNzAxODEzNy4xNjU3MDA1MzY0*_ga_QSFTKCEH7C*MTcwNDM2MTEyNi4zNi4wLjE3MDQzNjExMjYuNjAuMC4w*_ga_9JTEWVX24V*MTcwNDM2MTEyNi4zNi4wLjE3MDQzNjExMjYuNjAuMC4w
[23] European Medicines Agency, 'Qualification of novel methodologies for medicine development'. Accessed: Nov. 30, 2023. [Online]. Available: https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance/qualification-novel-methodologies-medicine-development-0
[24] J. Cummings, Y. Zhou, G. Lee, K. Zhong, J. Fonseca, and F. Cheng, 'Alzheimer's disease drug development pipeline: 2023', *A&D Transl Res & Clin Interv*, vol. 9, no. 2, p. e12385, Apr. 2023, doi: 10.1002/trc2.12385.
[25] H. Hampel *et al.*, 'Designing the next-generation clinical care pathway for Alzheimer's disease', *Nat Aging*, vol. 2, no. 8, pp. 692–703, Aug. 2022, doi: 10.1038/s43587-022-00269-x.
[26] K. Blennow, 'Phenotyping Alzheimer's disease with blood tests', *Science*, vol. 373, no. 6555, pp. 626–628, Aug. 2021, doi: 10.1126/science.abi5208.
[27] N. J. Ashton *et al.*, 'Plasma and CSF biomarkers in a memory clinic: Head-to-head comparison of phosphorylated tau immunoassays', *Alzheimer's & Dementia*, p. alz.12841, Nov. 2022, doi: 10.1002/alz.12841.
[28] X. Gong *et al.*, 'Is liquid biopsy mature enough for the diagnosis of Alzheimer's disease?', *Front. Aging Neurosci.*, vol. 14, p. 977999, Aug. 2022, doi: 10.3389/fnagi.2022.977999.
[29] A. Leuzy, N. Mattsson-Carlgren, S. Palmqvist, S. Janelidze, J. L. Dage, and O. Hansson, 'Blood-based biomarkers for Alzheimer's disease', *EMBO Mol Med*, vol. 14, no. 1, Jan. 2022, doi: 10.15252/emmm.202114408.
[30] E. Camporesi *et al.*, 'Fluid Biomarkers for Synaptic Dysfunction and Loss', *Biomark*[illegible]*Insights*, vol. 15, p. 117727192095031, Jan. 2020, doi: 10.1177/1177271920950319.
[31] E. Morenas-Rodríguez *et al.*, 'Soluble TREM2 in CSF and its association with other biomarkers and cognition in autosomal-dominant Alzheimer's disease: a longitudinal observational study', *Lancet Neurol*, vol. 21, no. 4, pp. 329–341, Apr. 2022, doi: 10.1016/S1474-4422(22)00027-8.
[32] N. Ogonowski *et al.*, 'Systematic Review: microRNAs as Potential Biomarkers in Mild Cognitive Impairment Diagnosis', *Front. Aging Neurosci.*, vol. 13, p. 807764, Jan. 2022, doi: 10.3389/fnagi.2021.807764.
[33] N. Z. Abuelezz, F. E. Nasr, M. A. AbdulKader, A. R. Bassiouny, and A. Zaky, 'MicroRNAs as Potential Orchestrators of Alzheimer's Disease-Related Pathologies: Insights on Current Status and Future Possibilities', *Front. Aging Neurosci.*, vol. 13, p. 743573, Oct. 2021, doi: 10.3389/fnagi.2021.743573.
[34] W. S. Liang, L. H. Goetz, and N. J. Schork, 'Assessing brain and biological aging trajectories associated with Alzheimer's disease', *Front. Neurosci.*, vol. 16, p. 1036102, Oct. 2022, doi: 10.3389/fnins.2022.1036102.
[35] D. W. Belsky *et al.*, 'DunedinPACE, a DNA methylation biomarker of the pace of aging', *eLife*, vol. 11, p. e73420, Jan. 2022, doi: 10.7554/eLife.73420.
[36] M. R. Duggan, A. Lu, T. C. Foster, M. Wimmer, and V. Parikh, 'Exosomes in Age-Related Cognitive Decline: Mechanistic Insights and Improving Outcomes', *Front. Aging Neurosci.*, vol. 14, p. 834775, Mar. 2022, doi: 10.3389/fnagi.2022.834775.
[37] P. Reveglia *et al.*, 'Challenges in LC–MS-based metabolomics for Alzheimer's disease early detection: targeted approaches versus untargeted approaches', *Metabolomics*, vol. 17, no. 9, p. 78, Sep. 2021, doi: 10.1007/s11306-021-01828-w.
[38] A. Gallo, L.-E. Pillet, and R. Verpillot, 'New frontiers in Alzheimer's disease diagnostic: Monoamines and their derivatives in biological fluids', *Experimental Gerontology*, vol. 152, p. 111452, Sep. 2021, doi: 10.1016/j.exger.2021.111452.
[39] K. Kim, C. H. Lee, and C. B. Park, 'Chemical sensing platforms for detecting trace-level Alzheimer's core biomarkers', *Chem. Soc. Rev.*, vol. 49, no. 15, pp. 5446–5472, 2020, doi: 10.1039/D0CS00107D.
[40] J.-H. Cai *et al.*, 'Magnetic Resonance Texture Analysis in Alzheimer's disease', *Academic Radiology*, vol. 27, no. 12, pp. 1774–1783, Dec. 2020, doi: 10.1016/j.acra.2020.01.006.
[41] T. Toyonaga *et al.*, 'In Vivo Synaptic Density Imaging with 11C-UCB-J Detects Treatment Effects of Saracatinib in a Mouse Model of Alzheimer Disease', *J Nucl Med*, vol. 60, no. 12, pp. 1780–1786, Dec. 2019, doi: 10.2967/jnumed.118.223867.
[42] M. Xiong *et al.*, 'In vivo imaging of synaptic density with [11C]UCB-J PET in two mouse models of neurodegenerative disease', *Neuroimage*, vol. 239, p. 118302, Oct. 2021, doi: 10.1016/j.neuroimage.2021.118302.
[43] C. Czakó *et al.*, 'Retinal biomarkers for Alzheimer's disease and vascular cognitive impairment and dementia (VCID): implication for early diagnosis and prognosis', *GeroScience*, vol. 42, no. 6, pp. 1499–1525, Dec. 2020, doi: 10.1007/s11357-020-00252-7.
[44] A. Song, N. Johnson, A. Ayala, and A. C. Thompson, 'Optical Coherence Tomography in Patients with Alzheimer's Disease: What Can It Tell Us?', *EB*, vol. Volume 13, pp. 1–20, Jan. 2021, doi: 10.2147/EB.S235238.

[45] E. Chalkias, F. Topouzis, T. Tegos, and M. Tsolaki, 'The Contribution of Ocular Biomarkers in the Differential Diagnosis of Alzheimer's Disease versus Other Types of Dementia and Future Prospects', *JAD*, vol. 80, no. 2, pp. 493–504, Mar. 2021, doi: 10.3233/JAD-201516.
[46] L. Toth *et al.*, 'A Speech Recognition-based Solution for the Automatic Detection of Mild Cognitive Impairment from Spontaneous Speech', *Curr Alzheimer Res*, vol. 15, no. 2, pp. 130–138, 2018, doi: 10.2174/1567205014666171121114930.
[47] S. Ahmed, A.-M. F. Haigh, C. A. de Jager, and P. Garrard, 'Connected speech as a marker of disease progression in autopsy-proven Alzheimer's disease', *Brain*, vol. 136, no. Pt 12, pp. 3727–3737, Dec. 2013, doi: 10.1093/brain/awt269.
[48] G. Fagherazzi, A. Fischer, M. Ismael, and V. Despotovic, 'Voice for Health: The Use of Vocal Biomarkers from Research to Clinical Practice', *Digit Biomark*, vol. 5, no. 1, pp. 78–88, Apr. 2021, doi: 10.1159/000515346.
[49] 'Summary of the European public assessment report (EPAR) for Prometax (rivastigmine)'. [Online]. Available: https://www.ema.europa.eu/en/documents/overview/prometax-epar-summary-public_en.pdf
[50] 'summary of the European public assessment report (EPAR) for Ebixa (memantine hydrochloride)'. [Online]. Available: https://www.ema.europa.eu/en/documents/overview/ebixa-epar-summary-public_en.pdf
[51] Food and Drug Administration, 'Biologics license application accelerated approval for Aduhelm (aducanumab-avwa)', Jun. 2021. [Online]. Available: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2021/761178Orig1s000ltr.pdf
[52] 'biologics license application accelerated approval for Leqembi (Lecanemab-irmb)'. [Online]. Available: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2023/761269Orig1s000ltr.pdf
[53] 'FDA Converts Novel Alzheimer's Disease Treatment to Traditional Approval'. Accessed: Oct. 26, 2023. [Online]. Available: https://www.fda.gov/news-events/press-announcements/fda-converts-novel-alzheimers-disease-treatment-traditional-approval
[54] Food and Drug Administration, 'FDA approves treatment for adults with Alzheimer's disease'. [Online]. Available: https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-treatment-adults-alzheimers-disease#:~:text=The%20U.S.%20Food%20and%20Drug,studied%20in%20the%20clinical%20trials.
[55] European Medicines Agency, 'Withdrawal Assessment report', Dec. 16, 2021. [Online]. Available: https://www.ema.europa.eu/en/documents/withdrawal-report/withdrawal-assessment-report-aduhelm_en.pdf
[56] 'Withdrawal of Aduhelm (aducanumab) 100 mg/mL concentrate for solution for infusion, EMEA/H/C/005558'. [Online]. Available: https://www.ema.europa.eu/en/documents/withdrawal-letter/withdrawal-letter-aduhelm_en.pdf
[57] European Medicines Agency, 'Leqembi recommended for treatment of early Alzheimer's disease'. Accessed: Nov. 19, 2024. [Online]. Available: https://www.ema.europa.eu/en/news/leqembi-recommended-treatment-early-alzheimers-disease
[58] J. Cummings *et al.*, 'Alzheimer's disease drug development pipeline: 2022', *A&D Transl Res & Clin Interv*, vol. 8, no. 1, Jan. 2022, doi: 10.1002/trc2.12295.
[59] 'Alzheimer's disease drug development pipeline: 2021', doi: https://doi.org/10.1002/trc2.12179.
[60] J. Cummings, G. Lee, A. Ritter, M. Sabbagh, and K. Zhong, 'Alzheimer's disease drug development pipeline: 2020', *A&D Transl Res & Clin Interv*, vol. 6, no. 1, Jan. 2020, doi: 10.1002/trc2.12050.
[61] J. Cummings, G. Lee, A. Ritter, M. Sabbagh, and K. Zhong, 'Alzheimer's disease drug development pipeline: 2019', *Alzheimer's & Dementia: Translational Research & Clinical Interventions*, vol. 5, no. 1, pp. 272–293, Jan. 2019, doi: 10.1016/j.trci.2019.05.008.
[62] J. Cummings, G. Lee, A. Ritter, and K. Zhong, 'Alzheimer's disease drug development pipeline: 2018', *Alzheimer's & Dementia: Translational Research & Clinical Interventions*, vol. 4, no. 1, pp. 195–214, Jan. 2018, doi: 10.1016/j.trci.2018.03.009.
[63] L. zhijia, Y. Bo, Z. Shuangqian, L. Zhigang, and Z. Lan, 'Targeting protein kinases for the treatment of Alzheimer's disease: Recent progress and future perspectives', *European Journal of Medicinal Chemistry*, Sep. 2023, [Online]. Available: https://doi.org/10.1016/j.ejmech.2023.115817
[64] R. Guy and D. Offen, 'Promising Opportunities for Treating Neurodegenerative Diseases with Mesenchymal Stem Cell-Derived Exosomes', *Biomolecules*, vol. 10, no. 9, p. 1320, Sep. 2020, doi: 10.3390/biom10091320.
[65] Alzheimer Europe, 'Prevalence of dementia in Europe'. Accessed: Dec. 15, 2023. [Online]. Available: https://www.alzheimer-europe.org/dementia/prevalence-dementia-europe
[66] 'The History of Alzheimer's Disease | BrightFocus Foundation'. Accessed: Jun. 19, 2023. [Online]. Available: https://www.brightfocus.org/alzheimers/article/history-alzheimers-disease
[67] Brain Health Institute, 'FINGERS'. [Online]. Available: https://fbhi.se/
[68] T. Ngandu *et al.*, 'A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial', *Lancet*, vol. 385, no. 9984, pp. 2255–2263, Jun. 2015, doi: 10.1016/S0140-6736(15)60461-5.

[69] AIBL, 'Leading the way in Alzheimer's disease research'. Accessed: Jan. 30, 2023. [Online]. Available: https://aibl.org.au/
[70] N. Avenue, 'What Are The Politicians Doing About Alzheimer's?', Forbes. Accessed: Jun. 19, 2023. [Online]. Available: https://www.forbes.com/sites/nextavenue/2016/07/26/what-are-the-politicians-doing-about-alzheimers/
[71] H. Gleckman, 'The Obama Administration's War on Alzheimer's', Forbes. Accessed: Jun. 19, 2023. [Online]. Available: https://www.forbes.com/sites/howardgleckman/2012/01/11/the-obama-administrations-war-on-alzheimers/
[72] '"France has not invested enough to prepare for the threat posed by Alzheimer's disease"', *Le Monde.fr*, May 20, 2022. Accessed: Jun. 19, 2023. [Online]. Available: https://www.lemonde.fr/en/opinion/article/2022/05/20/france-has-not-invested-enough-to-prepare-for-the-threat-posed-by-alzheimer-s-disease_5984098_23.html
[73] K. A. Dolan, 'Bill Gates Is Reupping His Commitment To Alzheimer's Research And Detection', Forbes. Accessed: Jun. 19, 2023. [Online]. Available: https://www.forbes.com/sites/kerryadolan/2022/07/30/bill-gates-is-reupping-his-commitment-to-alzheimers-research-and-detection/
[74] 'National Plan to Address Alzheimer's Disease: 2022 Update', ASPE. Accessed: Jun. 19, 2023. [Online]. Available: https://aspe.hhs.gov/reports/national-plan-2022-update
[75] 'World Dementia Council: Leading the Global Action Against Dementia'. Accessed: Oct. 25, 2023. [Online]. Available: https://www.worlddementiacouncil.org/
[76] Food and Drug Administration, 'Early Alzheimer's Disease: Developing Drugs for Treatment', Feb. 2018. [Online]. Available: https://www.fda.gov/media/110903/download
[77] Food and Drug Administration, 'Guidance for Industry Alzheimer's Disease: Developing Drugs for the Treatment of Early Stage Disease', Feb. 2013. [Online]. Available: https://isctm.org/public_access/FDAGuidance_AD_Developing_Drugs_Early_Stage_Treatment.pdf
[78] Food and Drug Administration, 'Human Gene Therapy for Neurodegenerative Diseases', Oct. 2022. [Online]. Available: https://www.fda.gov/media/144886/download
[79] Critical Path Institute, 'Critical Path for Alzheimer's Disease'. Accessed: Apr. 01, 2024. [Online]. Available: https://c-path.org/programs/cpad/
[80] S. Saunders, S. gregory, M. H. S. Clement, C. Birck, and S. van der Geyten, 'The European Prevention of Alzheimer's Dementia Programme: An Innovative Medicines Initiative-funded partnership to facilitate secondary prevention of Alzheimer's disease dementia', vol. 13, Nov. 2022, doi: 10.3389/fneur.2022.1051543.
[81] 'European Prevention of Alzheimer's Dementia Consortium'. Accessed: Oct. 25, 2023. [Online]. Available: https://ep-ad.org/
[82] 'European Dementia Prevention Initiative'. Accessed: Oct. 25, 2023. [Online]. Available: https://www.edpi.org/
[83] 'The EU Joint Programme – Neurodegenerative Disease Research (JPND)'. [Online]. Available: https://www.alzheimer-europe.org/policy/eu-action/eu-joint-programming-neurodenegenerative-diseases
[84] European Brain Council's, 'Rethinking Alzheimer's Disease'. Accessed: Oct. 25, 2023. [Online]. Available: https://www.braincouncil.eu/projects/rethinking-alzheimers-disease/
[85] European Academy of Neurology, 'Priority Topics 2022-2024'. Accessed: Oct. 25, 2023. [Online]. Available: https://www.ean.org/research/ean-guidelines/about-ean-guidelines-for-neurologists/priority-topics-2022-2024
[86] European Medicines Agency, 'Consolidated 3-year work plan for the Central Nervous System Working Party (CNSWP)'. [Online]. Available: https://www.ema.europa.eu/en/documents/work-programme/central-nervous-system-working-party-cnswp-work-plan-2022-2024_en.pdf
[87] J. A. Hardy and G. A. Higgins, 'Alzheimer's Disease: The Amyloid Cascade Hypothesis', no. 5054, Oct. 1992, doi: 10.1126/science.1566067.
[88] E. Karran and B. De Strooper, 'The amyloid hypothesis in Alzheimer disease: new insights from new therapeutics', *Nature Reviews Drug Discovery*, vol. 21, no. 4, pp. 306–318, Apr. 2022, doi: 10.1038/s41573-022-00391-w.
[89] C. Piller, 'Blots on a field?', *Science*, vol. 377, no. 6604, pp. 358–363, Jul. 2022, doi: 10.1126/science.add9993.
[90] O. Hansson, 'Biomarkers for neurodegenerative diseases', *Nat Med*, vol. 27, no. 6, pp. 954–963, Jun. 2021, doi: 10.1038/s41591-021-01382-x.
[91] Dynamed, 'Alzheimer Dementia'. [Online]. Available: https://www.dynamed.com/condition/alzheimer-dementia
[92] National Institute on Aging (NIH), 'Understanding Different Types of Dementia'. [Online]. Available: https://www.nia.nih.gov/health/infographics/understanding-different-types-dementia
[93] W. J. Jansen *et al.*, 'Prevalence of cerebral amyloid pathology in persons without dementia: a meta-analysis', *JAMA*, vol. 313, no. 19, pp. 1924–1938, May 2015, doi: 10.1001/jama.2015.4668.

[94] W. J. Jansen *et al.*, 'Prevalence Estimates of Amyloid Abnormality Across the Alzheimer Disease Clinical Spectrum', *JAMA Neurol*, vol. 79, no. 3, pp. 228–243, Mar. 2022, doi: 10.1001/jamaneurol.2021.5216.
[95] S. P. Arnerić, V. D. Kern, and D. T. Stephenson, 'Regulatory-accepted drug development tools are needed to accelerate innovative CNS disease treatments', *Biochem Pharmacol*, vol. 151, pp. 291–306, May 2018, doi: 10.1016/j.bcp.2018.01.043.
[96] 'AlzForum'. [Online]. Available: https://www.alzforum.org/research-models
[97] R. Sims, M. Hill, and J. Williams, 'The multiplex model of the genetics of Alzheimer's disease', *Nat Neurosci*, vol. 23, no. 3, pp. 311–322, Mar. 2020, doi: 10.1038/s41593-020-0599-5.
[98] M. P. Vitek *et al.*, 'Translational animal models for Alzheimer's disease: An Alzheimer's Association Business Consortium Think Tank', *A&D Transl Res & Clin Interv*, vol. 6, no. 1, Jan. 2020, doi: 10.1002/trc2.12114.
[99] M. Dulewicz, A. Kulczyńska-Przybik, P. Mroczko, J. Kornhuber, P. Lewczuk, and B. Mroczko, 'Biomarkers for the Diagnosis of Alzheimer's Disease in Clinical Practice: The Role of CSF Biomarkers during the Evolution of Diagnostic Criteria', *IJMS*, vol. 23, no. 15, p. 8598, Aug. 2022, doi: 10.3390/ijms23158598.
[100] L. Feng, J. Li, and R. Zhang, 'Current research status of blood biomarkers in Alzheimer's disease: Diagnosis and prognosis', *Ageing Research Reviews*, vol. 72, p. 101492, Dec. 2021, doi: 10.1016/j.arr.2021.101492.
[101] N. Mattsson *et al.*, 'CSF biomarker variability in the Alzheimer's Association quality control program', *Alzheimer's & Dementia*, vol. 9, no. 3, pp. 251–261, May 2013, doi: 10.1016/j.jalz.2013.01.010.
[102] J. W. Vogel *et al.*, 'Four distinct trajectories of tau deposition identified in Alzheimer's disease', *Nat Med*, vol. 27, no. 5, pp. 871–881, May 2021, doi: 10.1038/s41591-021-01309-6.
[103] R. Ossenkoppele, R. van der Kant, and O. Hansson, 'Tau biomarkers in Alzheimer's disease: towards implementation in clinical practice and trials', *Lancet Neurol*, vol. 21, no. 8, pp. 726–734, Aug. 2022, doi: 10.1016/S1474-4422(22)00168-5.
[104] A. Termine *et al.*, 'Multi-Layer Picture of Neurodegenerative Diseases: Lessons from the Use of Big Data through Artificial Intelligence', *JPM*, vol. 11, no. 4, p. 280, Apr. 2021, doi: 10.3390/jpm11040280.
[105] M. Khojaste-Sarakhsi, S. S. Haghighi, S. M. T. F. Ghomi, and E. Marchiori, 'Deep learning for Alzheimer's disease diagnosis: A survey', *Artificial Intelligence in Medicine*, vol. 130, p. 102332, Aug. 2022, doi: 10.1016/j.artmed.2022.102332.
[106] International Coalition of Medicines Regulatory Authorities, 'Horizon Scanning Assessment Report – Artificial Intelligence'. Accessed: May 01, 2024. [Online]. Available: https://www.icmra.info/drupal/sites/default/files/2021-08/horizon_scanning_report_artificial_intelligence.pdf
[107] S. S. Assunção *et al.*, 'Meaningful benefits: a framework to assess disease-modifying therapies in preclinical and early Alzheimer's disease', *Alz Res Therapy*, vol. 14, no. 1, p. 54, Dec. 2022, doi: 10.1186/s13195-022-00984-y.
[108] A. Hartry *et al.*, 'Evaluation of what matters most in existing clinical outcomes assessments in Alzheimer's disease: Neuropsychiatry and behavioral neurology/treatment development and clinical trials', *Alzheimer's & Dementia*, vol. 16, no. S6, Dec. 2020, doi: 10.1002/alz.040100.
[109] F. Öhman, J. Hassenstab, D. Berron, M. Schöll, and K. V. Papp, 'Current advances in digital cognitive assessment for preclinical Alzheimer's disease', *Alz & Dem Diag Ass & Dis Mo*, vol. 13, no. 1, Jan. 2021, doi: 10.1002/dad2.12217.
[110] P. Battista, C. Salvatore, M. Berlingeri, A. Cerasa, and I. Castiglioni, 'Artificial intelligence and neuropsychological measures: The case of Alzheimer's disease', *Neuroscience & Biobehavioral Reviews*, vol. 114, pp. 211–228, Jul. 2020, doi: 10.1016/j.neubiorev.2020.04.026.
[111] H. Hampel, J. Cummings, K. Blennow, P. Gao, C. R. Jack, and A. Vergallo, 'Developing the ATX(N) classification for use across the Alzheimer disease continuum', *Nat Rev Neurol*, vol. 17, no. 9, pp. 580–589, Sep. 2021, doi: 10.1038/s41582-021-00520-w.
[112] A. P. Owens *et al.*, 'Selecting Remote Measurement Technologies to Optimize Assessment of Function in Early Alzheimer's Disease: A Case Study', *Front. Psychiatry*, vol. 11, p. 582207, Nov. 2020, doi: 10.3389/fpsyt.2020.582207.
[113] Taskforce Horizon Scanning of the Beneluxa Initiative, 'Pharmaceutical Developments on Alzheimer's Disease'. Accessed: May 01, 2024. [Online]. Available: https://beneluxa.org/Alzheimer
[114] J. P. Hlavka, S. Mattke, and J. L. Liu, 'Assessing the Preparedness of the Health Care System Infrastructure in Six European Countries for an Alzheimer's Treatment', *Rand Health Q*, vol. 8, no. 3, p. 2, May 2019.
[115] J. L. Liss *et al.*, 'Practical recommendations for timely, accurate diagnosis of symptomatic Alzheimer's disease (MCI and dementia) in primary care: a review and synthesis', *J Intern Med*, vol. 290, no. 2, pp. 310–334, Aug. 2021, doi: 10.1111/joim.13244.
[116] J. van der Schaar *et al.*, 'Considerations regarding a diagnosis of Alzheimer's disease before dementia: a systematic review', *Alz Res Therapy*, vol. 14, no. 1, p. 31, Feb. 2022, doi: 10.1186/s13195-022-00971-3.

[117] C. H. van Dyck *et al.*, 'Lecanemab in Early Alzheimer's Disease', *N Engl J Med*, vol. 388, no. 1, pp. 9–21, Jan. 2023, doi: 10.1056/NEJMoa2212948.
[118] M. Prillaman, 'Heralded Alzheimer's drug works — but safety concerns loom', *Nature*, vol. 612, no. 7939, pp. 197–198, Dec. 2022, doi: 10.1038/d41586-022-04240-z.
[119] J. Couzin-frankel, 'New Alzheimer's drug clears FDA advisory vote despite unknowns', *Science*, Jun. 2024, doi: 10.1126/science.zbgh0es.
[120] A. de Wilde *et al.*, 'Disclosure of amyloid positron emission tomography results to individuals without dementia: a systematic review', *Alz Res Therapy*, vol. 10, no. 1, p. 72, Dec. 2018, doi: 10.1186/s13195-018-0398-3.
[121] 'IMI Alzheimer's projects issue guidance on giving biomarker info to research participants'. Accessed: Jun. 12, 2024. [Online]. Available: https://www.ihi.europa.eu/news-events/newsroom/imi-alzheimers-projects-issue-guidance-giving-biomarker-info-research
matic citation updates are disabled. To see the bibliography, click Refresh in the Zotero tab.