RETHINKING
ALZHEIMER'S DISEASE
DETECTION AND DIAGNOSIS

EBC
European Brain Council

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**For more information about "RETHINKING Alzheimer's disease",
please visit:** www.braincouncil.eu/projects/rethinking-alzheimers-disease/

☐ EXECUTIVE SUMMARY

Alzheimer's disease (AD), the most common form of dementia, is a progressive and debilitating neurodegenerative condition which robs people of their memory, their independence, their relationships and, ultimately, their lives. It affects close to 7 million people in the European Union (EU) alone[1]. AD is a growing public health issue with a huge burden for European economies, national healthcare and social care systems and a concern for the future.

Currently, the detection and diagnosis of AD relies on a system that remains focused on the late stage of the disease, despite a better understanding of the disease progression. Clinical practice and healthcare systems' readiness to detect, diagnose and treat the disease effectively are still lagging. While biomarkers are central to a diagnostic assessment for people with AD symptoms, the available detection and diagnostic tools such as cerebrospinal fluid tests (CSF) and positron emission tomography scans (PET), as well as relevant facilities are under-utilised.

To remove the barriers to early detection (at a pre-clinical stage, where it is believed that a therapeutic intervention could potentially halt or slow disease progression overall), the most urgent actions required are to foster an increased general awareness of the population about AD, improve professional education, and reduce stigma.This must be accompanied by a healthcare systems transformation, where the primary care professionals will play a greater role. The infrastructure for detection and diagnosis should also be improved by matching healthcare workforce and services, by greater adoption, availability and access to biomarkers and by an increase in the number of specialists. The promising results of moving towards a more coordinated care management approach involving all strands of disciplines relevant to AD must also be considered.

In addition, and in light of emerging detection and diagnosis modalities, as well as disease-modifying treatments (DMTs), more research on how biomarkers should be used for diagnosing AD in a clinical setting should be considered. Disclosing biomarkers results and related risk to people living with AD should also be improved.

Lastly, instruments to enhance access to early diagnosis are patient registries and databases as well as national dementia plans. The former are key elements to better understand the disease and develop clinical research. They also improve the lives of people living with AD and their healthcare planning. The latter must be developed in concertation with all stakeholders to ensure they cover all priorities, including awareness raising, education, flexibility to take stock of innovation and dedicated funding for implementation.

The policy recommendations gathered in this White Paper provide solid directions on how to rethink the detection and diagnosis of AD to help overcome the current challenges and be prepared to embrace innovation.

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[1] Gustavsson A, Norton N, Fast T, et al. Global estimates on the number of persons across the Alzheimer's disease continuum. Alzheimer's Dement. 2022;1-13. 13. https://doi.org/10.1002/alz.12694

☐ FOREWORD

AD is a significant and growing public health issue[3] with staggering costs, mostly due to the burden of informal, unpaid caregiving, and lost productivity.[4-5] The impact of this devastating disease falls inequitably on women, who are not only at greater risk of developing AD than men, but are also more likely to act as caregivers.[6]

There is no single path for the progression of AD, and it is not possible to predict how long a person with the disease will be able to live independently. Today, we know that AD is a continuum, consisting of an "at-risk phase" (pre-clinical stage - defined by AD biomarker positivity in asymptomatic individuals), a "Mild Cognitive Impairment (MCI) due to AD" or prodromal phase, and "dementia", which can be further classified in mild, moderate or severe.[7]

We are now at a crossroad with regards to the detection, diagnosis and management of the disease: it is thus crucial to acknowledge the true burden of the disease and aim to develop strategies to ensure that the healthcare systems are better equipped and prepared for people with AD in order to benefit from innovative solutions once they become approved for use.

Given that timely detection and diagnosis are crucial for disease management, and based on a sample of five EU countries (Czech Republic, Germany, Italy, the Netherlands and Sweden), the European Brain Council's (EBC) "RETHINKING Alzheimer's disease: Detection and diagnosis" project examines the challenges that need to be overcome in the EU to ensure the health care systems are appropriately equipped to provide timely and accurate diagnosis to those who may benefit most from new diagnostic tools and therapies. To develop its project led by EBC and supported and funded by the EFPIA Alzheimer's Platform composed of Biogen, Eli Lilly, Eisai, Novo Nordisk and Roche, EBC has organised interviews with experts from the selected 5 EU countries, as well as an online survey and a webinar to gather expertise that would help populate the policy recommendations supporting the project.

This project is one of EBC's 'Rethinking the management of brain disorders' projects. These projects respond to the clear need to rethink the management of brain disorders and redesign the care pathways to ensure optimal treatment and care for all people living with brain disorders in Europe. Their aim is to present a consensus on what needs to be achieved to resolve the most pressing challenges in brain conditions, today, and in the future, while also developing policy priorities around challenges in brain disorders.

Prof. Suzanne Dickson
President, European Brain Council

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[3] Bradford A, Kunik ME, Schulz P, Williams SP, Singh H. Missed and delayed diagnosis of dementia in primary care: prevalence and contributing factors. Alzheimer Dis Assoc Disord. 2009 Oct-Dec;23(4):306-14. doi: 10.1097/WAD.0b013e3181a6bebc. PMID: 19568149; PMCID: PMC2787842.

[4] Alzheimer's Disease International. Dementia Statistics. Available at: https://www.alzint.org/about/dementia-facts-figures/dementia-statistics/.

[5] Abbas A, Monfared T, Byrnes MJ. The Humanistic and Economic Burden of Alzheimer's Disease. Neurol Ther. 2022. doi.org/10.1007/s40120-022-00335-x

[6] Alzheimer's Disease International, Women and Dementia - A global research review, 2015, https://www.alzint.org/resource/women-and-dementia-a-global-research-review/

[7] Mayo Clinic. Alzheimer's disease. Available at: https://www.mayoclinic.org/diseases-conditions/alzheimers-disease/in-depth/alzheimers-stages/art-20048448. Last accessed: July 2022

☐ CALL TO ACTION: POLICY RECOMMENDATIONS

We call on policymakers to drive national, EU and international policies that can improve the lives of people living with AD, and ensure health systems are better prepared to support early detection and diagnosis now, and when future innovative detection and diagnostic tools and therapies become available.

There is a strong need to support the creation of a new environment that will:

1	**Recognise and act upon the benefits of early detection of AD**

2	**Improve local, regional and national access to already available and essential biomarker-based confirmatory diagnostic tests**

3	**Develop guidelines for the standardised adoption and implementation of advanced diagnostic tools to be implemented in clinical practice**

National level	• **Make dementia a national public health priority: develop, adequately fund, and implement a national dementia strategy**
	• involve people living with AD and health professionals to work alongside ministries of health, social affairs, education, research, industry to develop and allocate relevant funding to the strategy
	• raise awareness about dementia to reduce stigma and engage people living with AD to consult
	• educate and empower health professionals to feel confident in detecting and diagnosing the disease
	• include early detection and timely diagnosis in the strategy and raise awareness about the value of early management of the disease
	• ensure the strategy is flexible enough to give people living with AD swift access to innovation
	• support the implementation of a structured and sustainable care pathway supported by clear guidelines and taking stock of innovative detection and diagnostic tools and therapeutic innovation
	• adequately fund the national plan to allow implementation
	• **Make use of EU funding opportunities to improve national AD detection and diagnosis facilities and allow people with AD to benefit swiftly from innovation** (EU Recovery Plan or EU structural funds)
	• **Include gender mainstreaming in all policies** (to make progress in precision / personalised medicine, health and gender equity)

"My story is a story of voice and rights. Having received an early diagnosis has enabled me to become an advocate for those living with AD, to ensure their voice is heard and that they are involved. We have the experience. It is important that law makers understand and act upon our needs."

Helen Rochford-Brennan, Irish Dementia Working Group

European level

EUROPEAN COMMISSION

- **Develop, adequately fund and implement a substantial European Beating Dementia Plan** (building on the learnings off of the EU Beating Cancer Plan)
- **Foster educational and awareness campaigns about the importance of a timely detection and an accurate AD diagnosis** (to support national actions on AD)
- **Make full use of EU health and research programmes funding to improve detection and diagnosis of AD** (supporting education programmes, medical and social research, real-world application of the new detection and diagnostic tools - including blood-based biomarkers, precision / personalised medicine, gender equity)
- **Facilitate exchange of best practices among member states** (EU Joint Actions on AD, setting-up of an EU AD registry and a standardised set of statistics to regularly report for each country as an epidemiological surveillance of AD)

European level

EUROPEAN PARLIAMENT

- **Support calls to make dementia an EU health, social and research priority** (calling inter alia for an EU Beating AD Plan that would fill a gap and comprehensively address these priorities)
- **Support awareness campaigns and calls about the importance of a timely and accurate AD diagnosis** (in collaboration with national and European patients organisations, carers and family associations, health professionals, etc.)
- **Become an AD Ambassador** (through Members of the European Parliament engagement at European and national level)

"To address the plurality of skills needed to detect and diagnose AD, to learn from evidenced-based data to improve the healthcare systems, the public/private partnerships of the Innovative Health Initiative now involving three sectors of industry have the potential to support Member States' healthcare systems readiness to embrace innovation."

Andrzej Rys, Directorate-General for Health and Food Safety (DG SANTE), European Commission

"Looking at the magnitude of the disease, we need EU cooperation and knowledge to develop an EU AD programme. We need to create an EU model to support global action on early diagnosis, treatment and independent living support for all those affected by AD."

Sirpa Pietikäinen, Member of the European Parliament, (EPP, Finland)

"Collaboration, increase in research funding, sharing of information and best practice: let's learn from the achievements reached during the COVID-19 pandemic and from the EU Beating Cancer Plan. We now know that we can achieve a lot though collaboration. It's now time to put dementia and AD at the centre stage."

Deirdre Clune, Member of the European Parliament, (EPP, Ireland)

> *"Let's build on the EU financial and regulatory instruments to improve the detection and diagnosis of AD: EU research funding with Horizon Europe, Member States medical infrastructure and workforce development with the Cohesion Funds and the EU Recovery Plan, incentives for discovery of new treatments followed by swift and equal access to patients across the EU with the Pharmaceutical legislation, exchange of comparable data to increase innovation with the European Health Data Space."*

Tomislav Sokol, Member of the European Parliament, (EPP, Croatia)

International level	• **Collaborative AD health system and implementation research efforts*** (to reach consensus on research efforts and make recommendations for swift innovation uptake) ** Davos Alzheimer's Collaborative (DAC) looking inter alia at health systems preparedness and building on the findings of the DAC Learning Laboratory[10], World Dementia Council (WDC)[11], World Health Organization (WHO) Global action plan on the public health response to dementia 2017 -2025[12], Global Dementia Observatory[13], Intersectoral global action plan on epilepsy and other neurological disorders 2022-2031[14]*

> *"Detection and diagnosis of dementia is a WHO priority. WHO will continue monitoring the targets of dementia action plan through the Global Dementia Observatory and address the barriers and challenges."*

Dr Neerja Chowdhary, World Health Organization

☐ LIST OF ENDORSERS

To help improve the quality of life and care for people living with AD in Europe, the following organisations endorse the RETHINKING Alzheimer's disease White Paper, including the call to action and policy recommendations.

European Academy of Neurology,
Austria

European Institute of Women's Health,
Ireland

Masaryk University, Faculty of Medicine,
Czech Republic

Memory Center of the University Hospitals of Geneva,
Switzerland
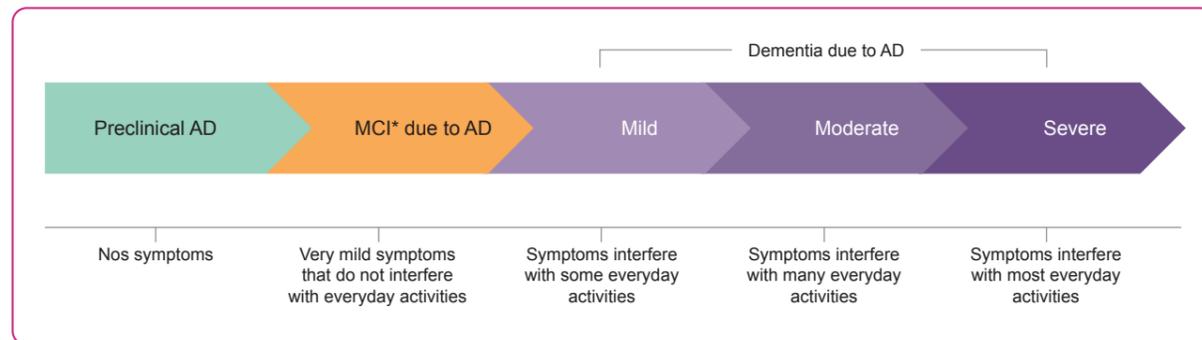
St. Anne's University Hospital Brno,
Czech Republic

University of Geneva,
Switzerland

Women's Brain Project,
Switzerland

ALZHEIMER'S DISEASE IN THE EUROPEAN UNION

AD is thought to contribute to 60-70% of dementia cases worldwide.[2] European estimates show 6.9 million people presenting with AD, 15 million with MCI, and 52 million with preclinical AD, together constituting 25% of all Europeans aged 50 and above.[15]

Preclinical AD	MCI* due to AD	Mild	Moderate	Severe
Nos symptoms	Very mild symptoms that do not interfere with everyday activities	Symptoms interfere with some everyday activities	Symptoms interfere with many everyday activities	Symptoms interfere with most everyday activities

Dementia due to AD

Alzheimer's Disease Continuum[16]

	2019				2025			
PREVALENCE OF DEMENTIA in the 5 EU countries covered in the paper[17]								
	Men	Women	Total	% of Population	Men	Women	Total	% of Population
Czech Republic	46 338	103 295	149 633	1,41	59 910	121 530	181 440	1,69
Germany	511 050	1 074 115	1 585 166	1,91	609 950	1 204 392	1 814 342	2,17
Italy	402 965	876 402	1 279 366	2,12	475 700	984 870	1460 570	2,44
Netherlands	87 292	169 239	256 532	1,49	116 455	200 625	317 080	1,83
Sweden	58 222	110 021	168 243	1,66	71 560	124 264	195 824	1,89

AD is not and nor should be considered as a normal part of ageing. It is a debilitating and progressive neurodegenerative disease: starting from the early stages of cognitive impairment, the condition leads to severe emotional, social, psychological and practical challenges for those affected, changing the course of their later life by reducing life expectancy and time living independently.[5-18] The dependence of those living with dementia increases as the disease progresses, and worldwide, dementia accounts for 11.9% of the years lived with disability due to a non-communicable disease.[12]

Age is however a risk factor for dementia. With the ageing of the population, the prevalence of people with dementia will increase in the years to come. The misconception that cognitive decline is an inevitable consequence of ageing and the perception that a formal diagnosis has no therapeutic consequences contribute to a lack of willingness to further investigate. As a result, healthcare professionals do not develop or maintain skills and workflows for evaluation of memory complaints, resulting in a vicious cycle of underdiagnosis.[19]

The severity of dementia is an important driver of cost. AD is a huge burden for European economies, and national healthcare and social care systems still lack the capacity to detect, diagnose and treat the disease effectively. The economic impact of dementia is substantial and growing. In the EU, the societal and economic cost of dementia is estimated to increase over EUR 250 billion by 2030 (with over 5% of this increase due to informal care costs), the equivalent of the whole GDP of Finland.[20] Both direct and indirect costs of dementia in European countries have become a significant and growing share of healthcare spending.[21] The majority of these costs are related to the round the clock care provided for people with dementia in nursing homes, home- and hospital-based care.[21]

Dementia disproportionately affects women and certain minority communities, contributing to health inequalities.[22-23] Women are not only at greater risk of AD than men, but are also more likely to act as caregivers.[6]

Approximately two-thirds of people with AD are women, and the lifetime risk of dementia is higher in women. This highlights the importance of a timely diagnosis as well as of an early understanding and management of risk factors in women.[24] Sex (biological) and gender (socio-cultural) differences in AD play a crucial role not only with regards to prevalence and incidence of the disease, but also in terms of risk factors, biomarkers, symptoms onset and symptoms characteristic. These sex and gender differences in AD are particularly relevant in the individual's diagnostic pathway and care journey,[25] as among others, the prognostic and diagnostic value of biomarkers may be different between men and women.

Research on different ethnic communities in the UK suggests that dementia prevalence is high in African-Caribbean and South Asian populations.[23] It is also high in Irish and Jewish ethnic groups in the UK as they are demographically older populations. There is also evidence that minority ethnic caregivers are more likely to be isolated from mainstream services, due to shame or stigma surrounding AD, particularly within Islam, Hindu and Sikh communities,[22] as among others, the prognostic and diagnostic value of biomarkers may be different between men and women.

"When we talk about early diagnosis and early treatment, we talk about supporting millions of women in the world to contribute to society. This holds a gender and health equity dimension."

Maria Teresa Ferretti, Women's Brain Project

Women and MCI[24]

According to published studies, mild cognitive impairment (MCI) is more common in men. Its diagnosis however is often missed in women or occurs at an advanced pathological stage; arguably or inferentially the incidence of MCI may also be higher in women than is appreciated. This is partly due to sex differences in neuropsychological tests, which rely heavily on verbal memory, and where women perform on average better than men, despite equal amounts of AD pathology.

Adjusting the cut-offs based on sex-specific considerations can assist in detecting approximately 20% more women who missed out an MCI diagnosis.

In addition to biological differences, MCI is often overlooked in women as gender stereotypes tend to steer diagnosis towards depression rather than MCI due to AD.

The ageing of the population will lead to a greater number of people developing AD and will affect the workforce, especially the number of physicians, specialists and nurses that will be needed to look after these people. Innovation in detection and diagnosis will call for collaboration between all sectors. Research will need to be integrated into the new diagnostic pathway.
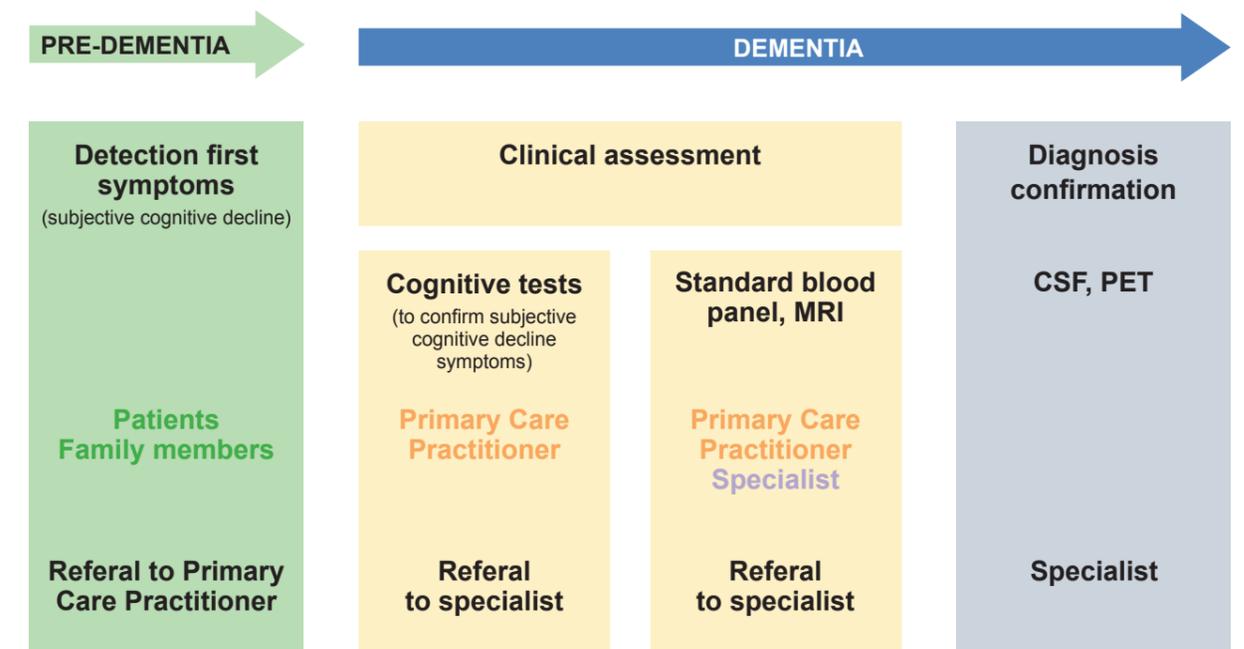
CURRENT DETECTION AND DIAGNOSTIC PATHWAY

Currently, the detection and diagnosis of AD relies heavily on a system that still focuses on the late stage of the disease, despite a better understanding of the disease progression now existing. The information gathered from the experts involved in the project and the webinar concludes that the healthcare systems in the EU are currently not equipped to diagnose AD early. The most urgent actions to readdress this are to foster general population awareness, improve professional education and reduce stigma. Then, to enable a timely and accurate detection and diagnosis of AD, the following improvements are necessary to identify: a sufficient infrastructure for diagnosis; the adoption, availability and access to biomarkers; and an increase in the number of specialists.

The diagnosis of AD is a combination of both cognitive tests and pathophysiological tests. Historically, the diagnosis and treatment of AD focused on clinical symptoms. Today, in-vivo biomarkers measured by CSF analysis or PET imaging at specialised and tertiary care are used to determine the core pathophysiological alterations that characterise AD across its preclinical and prodromal phases.[26] While research supports the use of CSF and PET to support a diagnosis of AD, access to these tools and their subsequent costs can vary greatly across geographies and healthcare systems.[27]

The advance in biomarker testing can also help rule out false-negative diagnosis of AD, thereby allowing people living with AD to access preventative measures and appropriate treatment earlier in the care pathway which may result in better quality of life and enable potential cost savings in long-term care.[28]

CURRENT DETECTION AND DIAGNOSIS PATHWAY

PRE-DEMENTIA	DEMENTIA		
Detection first symptoms (subjective cognitive decline)	**Clinical assessment**		**Diagnosis confirmation**
	Cognitive tests (to confirm subjective cognitive decline symptoms)	**Standard blood panel, MRI**	**CSF, PET**
Patients Family members	**Primary Care Practitioner**	**Primary Care Practitioner** **Specialist**	
Referal to Primary Care Practitioner	**Referal to specialist**	**Referal to specialist**	**Specialist**

The long road to a diagnosis

Across the EU, the journey to receiving a diagnosis of AD is still complex and plagued by a number of barriers with healthcare systems ill-equipped to detect AD. Dementia, especially in its early stages, remains under-detected, under-diagnosed, under-disclosed, and under-managed.[29]

"It can take months to have access to an appointment to get a diagnosis. If there is one thing that people with AD do not have, it is time. AD is the cancer of today. We need to do better, especially at MCI stage."

Helen Rochford-Brennan, Irish Dementia Working Group

It is estimated that 75% of worldwide dementia cases today are undiagnosed.[4] Up to 1 in 5 people clinically diagnosed with probable AD during their lifetime did not have AD pathology at autopsy,[30] and 50% of people with any form of dementia were not formally diagnosed.[31] A European survey shows that on average 20% of the people with dementia were not informed of their diagnosis, with the highest proportion in Italy (with a percentage of 59.3%).[32]

The diagnosis of dementia is all too often made late, when the symptoms are already far advanced. Caregivers of a person with dementia report having to wait one to two years before bringing the symptoms to the attention of a physician.[29] In the EU, the overall mean length of time between problems being noticed and the diagnosis being made can be up to 2.1 years (1.6 years in Italy and the Czech Republic and 2.6 years in the Netherlands).[32]

Stigma is a primary barrier to timely diagnosis and care.[33] Very few countries run awareness campaigns that provide information about the signs and symptoms of AD. When they do, these campaigns are not commensurate with the need. Awareness campaigns have been insufficient in size, scope and funding to eliminate stigma and reduce the fear of entering the diagnostic pathway.[33]

"Let's say good-bye to stigma and put all our efforts into awareness and education." **Helen Rochford-Brennan, Irish Dementia Working Group**

"We have normalised conversations about health disorders (diabetes, blood pressure…) but when it comes to the brain, there is huge stigma. We need to talk more openly about AD as we do for other conditions." **Maria Teresa Ferretti, Women's Brain Project**

The entry point to a diagnosis

At primary care level, little usually happens due to primary care practitioners' misconceptions about AD: they often associate progressive cognitive decline and/or changes in behaviour with normal ageing or depression, or rather confuse them with other mental illnesses. [24-34] Globally, almost 62% of healthcare providers think that dementia is part of normal aging.[35]

A recent survey showed that the healthcare professionals to be consulted for a diagnosis were family doctors (39%), followed by specialists (neurologists (29%), geriatricians (17%), psycho-geriatricians (6%)[24]. Many looked for information from the Internet before (29%), during (38%) and after (36%) the diagnostic assessment.[24]

When a general practitioner or family physician assesses the subjective cognitive decline symptoms of the patient using cognitive tests, the next step is usually to refer the person to a dementia specialist. It can be a neurologist, psychiatrist or geriatrician who will run a confirmatory neurocognitive testing and determine the aetiology of the disease, ideally after ruling out addressable causes like substance use, depression, and detecting possible structural causes such as a past stroke.[36] In people with confirmed cognitive decline, biomarker testing is required to ascertain the pathological hallmarks of AD.[36]

Many GPs do not receive enough training about AD and other dementias to facilitate diagnosis, identify early symptoms, and differentiate these symptoms from other disorders.[33] They have difficulty recognising the early symptoms of dementia or tend to overlook their importance, lack confidence in their ability to detect dementia, particularly in its early stages, and feel uninformed about available support services for the person living with AD and their care-givers post diagnosis.[29] Some GPs are reluctant to refer symptomatic people for formal diagnosis with a specialist out of concern that the lack of a DMT negates the value of diagnosis —so called "therapeutic nihilism".[33]

GPs currently deal with patients presenting with a number of diseases that need to be diagnosed early (cardiovascular diseases, diabetes…). Carrying initial cognitive testing hardly fits into the usual 10–15-minute GP visit. This results in primary care clinicians not developing or maintaining necessary skills and workflows for evaluation of memory complaints, resulting in a vicious cycle of underdiagnosis.[29-33]

Nevertheless, a European survey among carers revealed that when help was sought from a primary care practitioner, the timeframe before then seeing a specialist appeared to be quicker: more than three-quarters of the carers (79,3%) reported that the person with dementia had the first visit with the specialist doctor or service within 6 months of the first visit to their GP.[32]

An increasing number of individuals with normal cognitive performance also seek help in the current memory clinics asking an evaluation of their dementia risk, preventive interventions, or interventions to ameliorate their cognitive performance. Evidence suggests that some of these individuals are indeed at increased risk of dementia. However, current memory clinics do not have the programs and protocols in place to deal with this new population.[37]

Structural barriers

Despite being the entry point for most people living with AD, GPs lack access to the diagnostic tools required to make an initial diagnosis and competency to use them. Most people are still diagnosed using basic screening tools, which have high false (positive and negative) rates.[33] Those who already have access to basic screening tools may lack access to the more advanced diagnostics needed to move persons along the diagnostic pathway.[33] Also important to consider, the ratio of GPs to the general population is inadequate, placing GPs under great stress.[33]

The diagnostic infrastructure varies among the 5 EU countries studied in this report. In the EU, the specialists involved in diagnosing cognitive impairment and dementia vary in each country. For instance, in Sweden, geriatricians and psychiatrist are involved in diagnosis (rather than neurologists).[33] In Germany and Sweden, approximately 60% of psychiatrists would be involved in formal diagnosis of MCI due to AD, whereas the remaining 40% primarily practice psychotherapy.[26] The availability of the dementia specialist workforce to see people with MCI in the diagnostic phase depends on the capacity of each specialist to conduct the evaluations.[38]

Referral to a specialist who is crucial in making a formal diagnosis can take as long as three years due to a lack of available specialists. Several countries face chronic shortages of geriatricians, neurologists, psychiatrists, and other cognitive experts.[12-33]

The shortage of specialists is expected to worsen with the increase of ageing populations.[38] Country-specific workforce projections by specialty are scarce in publicly available reports,[38] and those available are limited to certain geographies, exhibiting different trends by specialties, and showing uncertainty in the projections.[38]

The EU 2020 Annual Report on shortage and surplus occupations show high magnitude medical workforce shortages for nursing professionals, general practitioners, health care assistants and associate professional nurses, as well as medical specialised practitioners. Denmark, Estonia, Finland, Luxembourg, the Netherlands, Norway, Romania, Slovenia and Spain particularly reported health professional shortages.[39]

"There is under-utilisation of the diagnostic techniques and services available today. Looking at the Swedish Dementia Registry, the share of patients who have been given an unspecified diagnosis has been reduced from about 50% to about 20%. Nevertheless, we need to see an increased use of biomarkers. There is value in having a correct or accurate diagnosis. The cost of a diagnosis process is still pretty small in the disease course."

Linus Jönsson, Karolinska Institutet

There are differences between countries regarding the diagnostic infrastructure and the availability of biomarkers. The currently available diagnostic facilities and tools are often not used to their potential or insufficient. In 2020, PET scanners were generally the least available and used across the EU.[40] Relative to population size, all of EU Member States (besides Denmark) present ratios of 0.5 units per 100,000 inhabitants or less (0.8 for Denmark).[42]
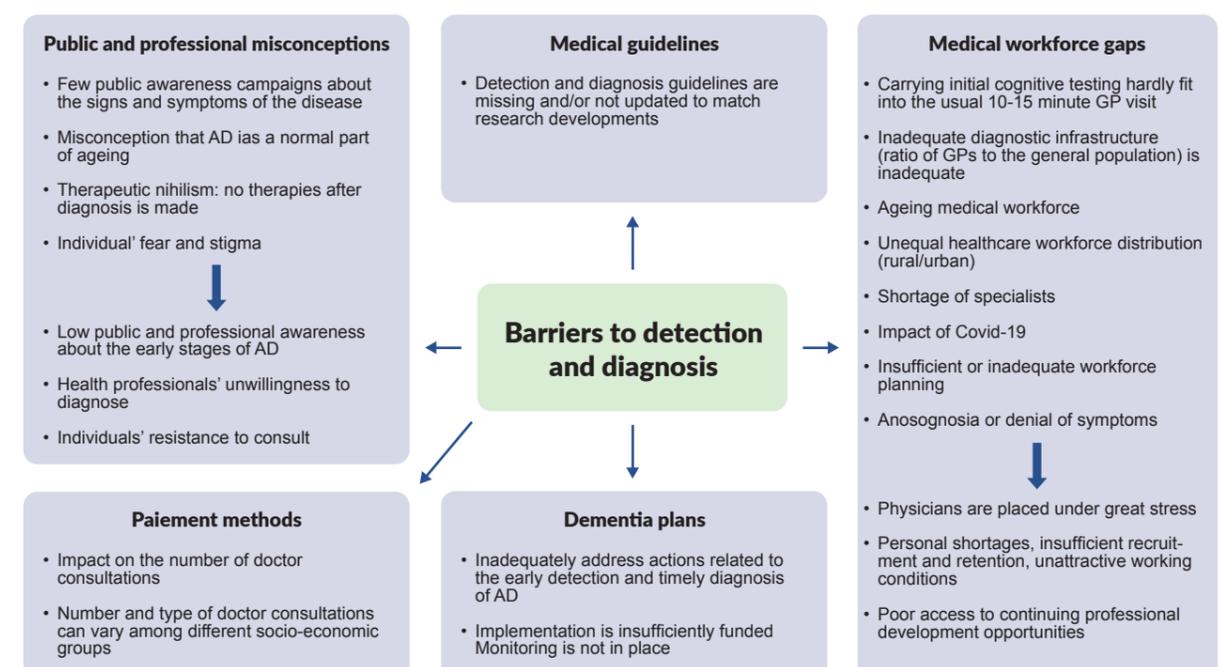
"The main infrastructure need is access to cognitive tests by neuropsychologists, scanners and CSF Dealing with biomarkers is highly specialised, the personnel must be equipped and educated to interpret them."

Maria Teresa Ferretti, Women's Brain Project

Provider payment methods and levels of co-payments have an impact on the number of doctor consultations. In the countries where doctors are paid predominantly by fee-for-service (as in Germany), there are higher consultation rates than those countries where doctors are mainly paid by salaries or capitation (as in Sweden). In these latter countries, patient co-payments are high for a large proportion of the population, which may result in individuals not consulting a doctor or delaying seeing a doctor because of the cost of care.[41]

The number and type of doctor consultations can vary among different socio-economic groups. Wealthier individuals are more likely to see a doctor than individuals in the lowest income quintile, for a comparable level of need. Income inequalities in accessing doctors are much more marked for specialists than for general practitioners.[33]

Public and professional misconceptions

- Few public awareness campaigns about the signs and symptoms of the disease
- Misconception that AD ias a normal part of ageing
- Therapeutic nihilism: no therapies after diagnosis is made
- Individual' fear and stigma
- Low public and professional awareness about the early stages of AD
- Health professionals' unwillingness to diagnose
- Individuals' resistance to consult

Medical guidelines

- Detection and diagnosis guidelines are missing and/or not updated to match research developments

Medical workforce gaps

- Carrying initial cognitive testing hardly fit into the usual 10-15 minute GP visit
- Inadequate diagnostic infrastructure (ratio of GPs to the general population) is inadequate
- Ageing medical workforce
- Unequal healthcare workforce distribution (rural/urban)
- Shortage of specialists
- Impact of Covid-19
- Insufficient or inadequate workforce planning
- Anosognosia or denial of symptoms
- Physicians are placed under great stress
- Personal shortages, insufficient recruitment and retention, unattractive working conditions
- Poor access to continuing professional development opportunities

Barriers to detection and diagnosis

Paiement methods

- Impact on the number of doctor consultations
- Number and type of doctor consultations can vary among different socio-economic groups

Dementia plans

- Inadequately address actions related to the early detection and timely diagnosis of AD
- Implementation is insufficiently funded Monitoring is not in place

☐ AIM OF THE RESEARCH

"Alzheimer's disease is a significant and growing public health issue that has been labelled as a major unmet medical need. This compels us to rethink how we detect and diagnose AD and prepare the healthcare systems to embrace the scientific advances. We owe this to the people with AD, their family and society as a whole."

Sirpa Pietikäinen, Member of the European Parliament

We are now at cross-roads in the earlier detection and diagnosis of AD. Delays in detection and diagnosis of AD can lead to irreversible worsening of the disease. Today, there is often no diagnosis or an uncertain diagnosis. The IDEAS study showed that AD diagnosis increased from 80.3% to 95.5% in people with a positive PET scan, and decreased from 71.5% to 10.2% in people with a negative scan.[42]

Obtaining a timely clinical and accurate pathological diagnosis can provide individuals with a better chance of engaging in dementia-associated risk factors prevention and managing co-morbid conditions, offering them the opportunity to participate in clinical trials and help both them and their families plan for the future.

In the future, as PET imaging is expensive and of limited availability, and CSF sampling may be considered invasive, the on-going research into DMTs and the rapidly advancing development of blood-based biomarkers (BBB) for AD are particularly promising to support early detection of AD, given the broad availability, scalability and cost-effectiveness of blood tests globally.[26]

This calls for a next-generation global framework of clinical care pathways for individuals with AD. Under this framework, new clinical pathways – which may differ by country and clinical context – must enable early detection and timely, accurate, and effective diagnosis at the early stages of MCI due to AD and mild AD dementia.[26]

☐ THE VALUE OF RETHINKING THE ALZHEIMER'S DISEASE DETECTION AND DIAGNOSTIC PATHWAY

While BBBs are in development and hold significant potential to support earlier detection of AD, they are still not available at scale. The only BBB that is commercially available is largely used in the research setting.

In the future, BBB could have two triage roles. One would be a 'rule out' role where they could be incorporated into primary care to determine patients' probability of having AD should be referred to secondary settings for more advanced biomarker-based investigations such as CSF or PET.[43] When BBB can demonstrate an accuracy similar to already existing tools (CSF and PET), they could rather have a 'rule in' role where they would replace CSF and PET and refer people with AD to treatment.

To assess the impact of early detection and timely, accurate diagnosis of AD in Europe, this project studied the health-economic effects of the implementation of BBBs tests in combination with cognitive tests, to improve triaging at the primary care level, compared to a 'usual' care scenario where only cognitive tests are used. We assessed the short-term impact on the cost of the detection and diagnostic process, and the relative balance of benefits and costs over a predicted 20-year time horizon of care needs using the Swedish healthcare setting as an example*.

This preliminary analysis showed that the use of BBB tests in combination with cognitive assessment in primary care can improve the efficiency of the evaluation process, increasing the number of correctly identified cases (i.e., patients with MCI due to AD) thereby reducing the number of 'unnecessary' (i.e., patients with no AD) referrals for more expensive (PET) or invasive (CSF) specialist evaluations. The improved triage is estimated to reduce specialist evaluations from 36% to 14% with an annual net cost saving of about EUR 4 million. Furthermore, providing BBB tests in combination with cognitive assessment in primary care would also help to improve the detection of people with a possible early stage of AD, allowing them to receive a timely diagnosis and access to the care pathway. Even considering currently available symptomatic treatment options, the resulting benefits equate to an increase of Quality Adjusted Life Years (QALYs) of 0.033, and a reduction of health and social care costs of EUR 1,062 per people living with AD (Net Present Value) over a 20-year time horizon.

This initial analysis suggests that a combination of a cognitive screening test and BBB tests have the potential to improve the efficiency of AD diagnostic process and access to treatment. Furthermore, it also shows that early diagnosis and access to current symptomatic treatment options can improve individuals' outcomes and reduce costs.

With the introduction of upcoming DMTs, BBB tests (or equivalent diagnostic tools that can be implemented at primary care level) can become a more important solution for reducing obstacles to access, and have an even greater impact on costs and patient outcomes.

Overall, improvements in the efficiency of the AD detection process at primary care level can reduce the overall burden on the healthcare system and ensure timely access to treatment in a potentially cost-saving way.
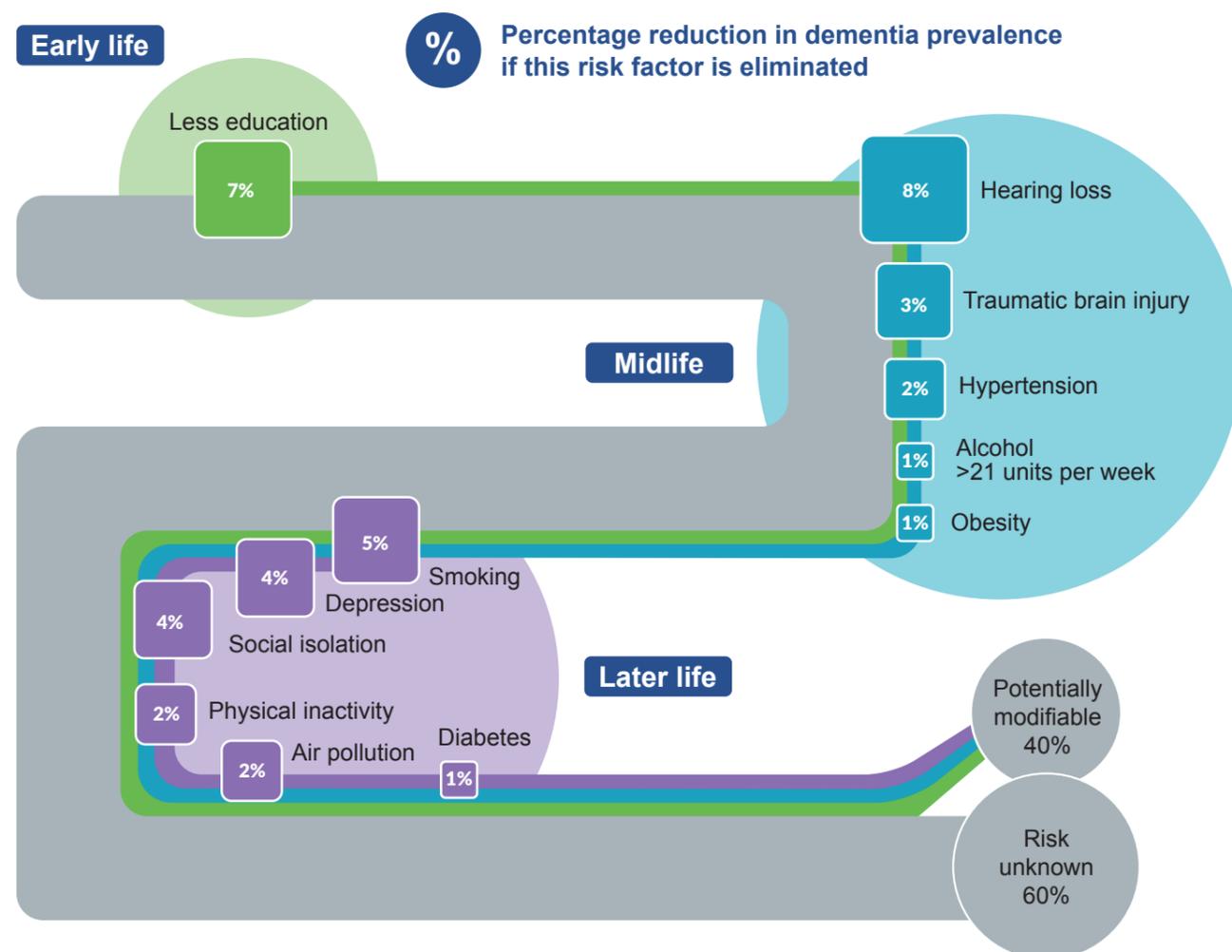
* Details of the economic evaluation are available here: technical report

** This is estimate considering the current MCI incidence in the Swedish population above 55 years. With the introduction of upcoming disease-modifying Alzheimer's treatment (DMT), it is expected that a larger number of people in that age range without MCI will seek assessment at primary care. In that case the projected net cost saving can go up to 185 million euro.

☐ MOVING TOWARDS A NEW ALZHEIMER'S DISEASE DETECTION AND DIAGNOSIS PATHWAY

Improving the detection and diagnosis of AD must start with filling the current gaps: under-utilisation of the detection and diagnosis tools and facilities available (CSF and PET), raising awareness of the general public (including healthcare professionals) about AD, its early signs and the value of an early diagnosis, delivering the necessary education to health professionals to equip them with detection and diagnosis skills.

Looking ahead, the re-conceptualisation of AD as a clinical and biological construct and the development of biomarker-guided targeted therapies call for the need to transition from the current clinical symptom-focused and late-stage diagnosis and management of AD to a new pathway that incorporates biomarker-guided and digital decision-making tools for risk stratification, early detection, timely diagnosis, and preventative or therapeutic interventions.[29] Based on an assessment of the healthcare systems in 6 EU countries (France, Germany, Italy, Spain, Sweden and the United Kingdom), this could translate into 7.1 million people living with ADs seeking evaluation by a dementia specialist, and 2.3 million of which may have MCI and can therefore be eligible for treatment.[12]
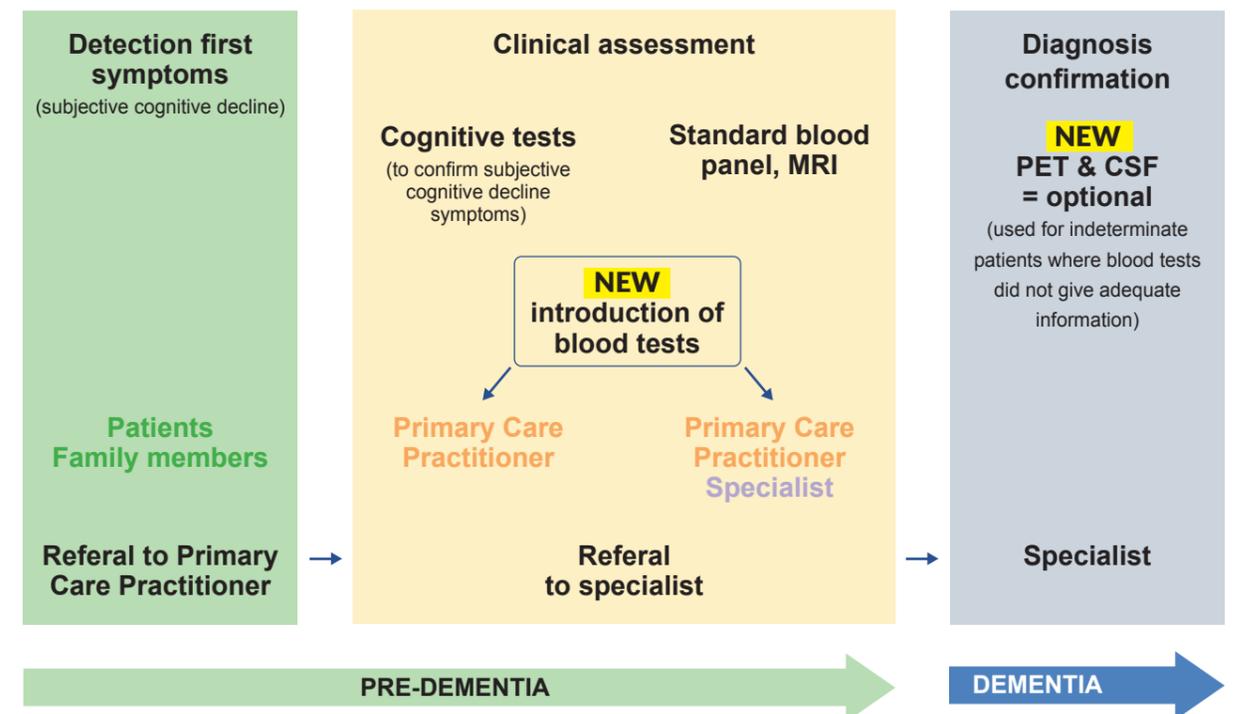
Early detection and diagnosis of AD can have repercussions on disease prevention giving the primary care practitioner a key role in raising awareness about the risk factors associated with AD. Evidence has identified 12 potentially modifiable risk factors for dementia: less education, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes, low social contact, excessive alcohol consumption, traumatic brain injury, and air pollution. Together these 12 modifiable risk factors account for around 40% of cases of worldwide dementias, which could theoretically be prevented or delayed.[44] Evidence has also shown that it is never too early and never too late in the life course for dementia prevention.[44]

The future detection and diagnostic pathway should focus on the pre-dementia stage, where people living with AD, as well as primary care practitioners, will be on the first line to detect AD in timely manner. In the future, besides carrying out cognitive tests, the primary care practitioner would ideally be able to use BBBs with increased accuracy. They would constitute a first line for primary care practitioners to decide to refer or not to refer to a second line memory clinic or specialised centre for confirmation ('triage role'). Using BBBs at the GP level may also be interesting to exclude AD and to promote the GPs to concentrate on other causes for the condition.

This will change the primary care practitioner's role and call for a healthcare system transformation where new opportunities for valuable prevention and risk reduction behaviours will become more salient, for which access to more accurate diagnostic tools will be pivotal.

Early life

% Percentage reduction in dementia prevalence if this risk factor is eliminated

Less education — 7%
Hearing loss — 8%
Traumatic brain injury — 3%
Hypertension — 2%
Alcohol >21 units per week — 1%
Obesity — 1%
Midlife
Smoking — 5%
Depression — 4%
Social isolation — 4%
Physical inactivity — 2%
Air pollution — 2%
Diabetes — 1%
Later life
Potentially modifiable 40%
Risk unknown 60%

NEW DETECTION AND DIAGNOSIS PATHWAY

Detection first symptoms (subjective cognitive decline)

Patients Family members

Referal to Primary Care Practitioner

Clinical assessment

Cognitive tests (to confirm subjective cognitive decline symptoms)

Standard blood panel, MRI

NEW introduction of blood tests

Primary Care Practitioner

Primary Care Practitioner Specialist

Referal to specialist

Diagnosis confirmation

NEW PET & CSF = optional (used for indeterminate patients where blood tests did not give adequate information)

Specialist

PRE-DEMENTIA

DEMENTIA

Moving towards a more precise diagnosis – The gender perspective[24]

Considering sex and gender differences is crucial in the development of detection and diagnosis solutions. Both sex (biological) and gender (socio-economic) factors can influence access to healthcare and accurate diagnosis of AD.

The use of biomarkers has the potential to overcome gender biases and leverage sex differences for a more precise diagnosis. There is growing evidence that the levels of several currently used biomarkers differ between men and women. For example, CSF concentration of neurofilament light chain, a biomarker for neurodegeneration, has been shown to be higher in men, while tau, another biomarker for neurodegeneration, was higher in women. Several PET-imaging studies also show that tau levels in the brain accumulate at higher levels and faster in women. This suggests that sex-specific cut-offs, for both diagnostic and prognostic value, should be carefully examined.

In the near future, when BBBs are used to detect at-risk individuals, it will be important to also consider sex-related aspects in the application of such biomarkers. To enable precision medicine, multidimensional data needs to be analysed and interpreted via predictive algorithms. In this context, sex and gender are crucial factors affecting the overall predictive power of clinical models. Indeed, it has been shown that including sex in predictive algorithms improves their efficiency.

There is still insufficient awareness of sex and gender influence on the diagnostic journey by the medical community and society overall. Considering sex- and gender-specific factors is a key step to improve access to and precision of diagnosis of AD, especially during early stages. A paradigm shift towards precision neurology will optimise the diagnostic pathway and the individual's medical journey.

"AD is the cancer of today. Precision medicine in cancer has tremendously improved patients' treatment. We should do the same for AD. By leveraging all aspects of sex and gender differences, considering multidimensional data and tailoring the approach to the person's needs, then we will diagnose AD earlier."
Maria Teresa Ferretti, Women's Brain Project

Healthcare systems transformation

"New diagnosis tools and treatments go in tandem. Collaboration between countries will be essential to understand how to use the new technologies to their full potential by following-up patients on a routine basis and sharing data and learnings."
Linus Jönsson, Karolinska Institutet

Some studies have warned that the existing healthcare systems are currently ill prepared: based on the hypothesis that a DMT becomes available, the current infrastructure to handle the potential caseload of MCI detection would lead to long waiting times for initial dementia specialist visits, followed by considerable waits for biomarker testing to further confirm. Delays like these could result in more than 1 million people developing AD while waiting for evaluation and treatment between 2020 and 2025.[15] This missed opportunity to improve the person's quality of life and postpone diagnosis can increase both the direct and indirect costs that are incurred at an advanced stage, and must be avoided. Ensuring scientific discovery that brings meaningful impacts to people living with AD requires health systems to strategically prepare for this innovation and integration of new interventions.[45]

Assessment tools typically used in clinical practice currently focus on measuring cognitive and functional decline over time, and are therefore less effective in the initial stages of the disease, when cognitive symptoms are subtle and functional impairment not yet evident.[46] In clinical practice, biomarkers will be central to a diagnosis assessment for individuals with symptoms of AD, alongside medical history, physical exams, laboratory tests and a range of neurological and neuropsychological tests of mental function.[47]

The introduction of BBBs testing (both at GP and specialist level) will only achieve their transformative potential if health systems can overcome infrastructure and economic barriers.[46]

Current memory clinics do not have the programs and protocols in place to deal with the increasing number of individuals with normal cognitive performance who ask for an evaluation of their dementia risk, preventive interventions, or interventions to ameliorate their cognitive performance. This new health demand asks for a shift of target population, from people with cognitive impairment to worried (but cognitively unimpaired) individuals. The answer to this challenge could be the development of new services offering a precision medicine approach, 'Brain Health Services', devoted to responding to demands from cognitively unimpaired individuals concerned about their risk of dementia. The Brain Health Services model would help address dementia risk profiling, dementia risk communication, dementia risk reduction, and cognitive enhancement.[37]

GPs' and specialists' greater role

GPs who would play a greater role in the detection and diagnosis of AD, are increasingly less hesitant about such a shift in care. A 2017 survey among primary care practitioners across 25 European countries found that the majority of individuals involved in dementia investigations and assessment. Variations between countries were explained by policy differences (such as the presence or absence of national dementia plans, and clinical practice, that is, the existence of clinical guidelines).[12] In a survey carried out among GPs, 74% of them stated that an early diagnosis was valuable, 58% were of the opinion that the benefit of early diagnosis outweighed the risk, and 59% said that they would change their implementation of early diagnosis if a drug were available to slow down the progression of AD.[48]

In leveraging GPs' increased interest in diagnosing AD, their identified education gaps on AD must be filled. The WHO has identified a set of actions to strengthen the health and care workforce. They include: aligning education with population needs and health service requirements, strengthening continuing professional development to equip the workforce with new knowledge and competencies, increasing public investment in workforce education, development and protection, optimising the use of funds through innovative workforce policies.[49]

Looking at how to increasingly involve primary care practitioners in the early detection of AD without overwhelming them, it is worthwhile to build on the current practices. Today, GPs deal with patients presenting with risk factors for AD (cardiovascular diseases, diabetes, etc.) that are routinely monitored. Moving towards a prevention work package at the primary care level that would include AD detection would represent a significant step forward. By extension, involving other professionals who follow individuals on a prevention routine basis (such as gynaecologists, ophthalmologists, etc.) should also be considered.

Healthcare workforce and services

To match the GPs' increased role, the ageing of the medical workforce also needs to be addressed. Some countries have seen a rapid ageing of their medical workforce over the past two decades. Italy is the most striking example with the share of doctors aged 55 and over increasing from about 20% in 2000 to 56% in 2019.[41] The highest proportion of younger physicians (under 35 years) can be seen in the Netherlands (31.4 %).[50] At the same time, changes in retirement patterns of doctors can be seen with many possibly continuing to practise beyond age 65, full time or part time, if the working conditions are adequate and if pension systems do not provide a disincentive for them to do so.[41]

A high concentration of doctors and specialised services can be seen in national capital regions. This is particularly the case in the Czech Republic and Germany.[41] Generally, there is a perceived shortage of specialists, which is expected to worsen with the ageing populations. For instance, in Germany, the National Association of Statutory Health Insurance Physicians predicted the number of neurologists to remain relatively stable through 2030, with fluctuation of ±3% between 2014 and 2030.[15] This stability will hinder the healthcare service from adapting to the need to diagnose an increased number of people presenting MCI.

The COVID-19 pandemic's toll on the countries' healthcare workforce is continuing at a time of acute economic crisis. Personnel shortages, insufficient recruitment and retention, migration of qualified workers, unattractive working conditions, and poor access to continuing professional development opportunities are blighting the healthcare systems.[41]

There is inadequate data and limited analytical capacity, poor governance and management, lack of strategic planning, and insufficient investment in developing the workforce. Very few countries report on healthcare workforces by urban/rural, hospital/primary healthcare and public/private distribution. Publicly available workforce projections are limited to certain geographies, exhibiting different trends by specialties, and showing uncertainty in the projections.

Proper health workforce planning and education is utmost required to ensure professionals are up-to-date with the scientific developments, and a sufficient number of GPs will be required to be able to triage individuals who will need to be directed to confirmatory testing.

WHO and dementia

The WHO Global action plan on the public health response to dementia 2017 – 2025[12] has a specific global target for dementia diagnosis of 50% of countries to reach a dementia diagnosis rate of at least 50%. Different tools can help the countries reach this target:

- The Mental Health Gap Action Programme (mhGAP) Intervention Guide[51] for doctors, nurses, other health workers as well as health planners and managers presents the integrated management of priority MNS conditions using algorithms for clinical decision making

- A blueprint for dementia research[52] that has a chapter on diagnosis. It identifies the current gaps and actions needed as well as specific milestones that can be achieved. It addresses the development of biomarkers, clinical assessment of cognition and functioning as well as diagnosis during the prodromal stage. Some work is being done on 'preferred product characteristics' for dementia diagnosis which focusses on fluid biomarkers.

Registries

Patient registries and databases are key elements to develop clinical research, to improve people living with AD care and healthcare planning. They are also vital to assess the feasibility of clinical trials, to facilitate the planning of appropriate clinical trials, and to help support the enrolment of people living with ADs. Eighty percent of clinical studies are delayed because too few people sign-up to participate.[53] Trials matching services exist: several Alzheimer associations have developed initiatives where volunteers register their interest in participating in trials and are matched with studies that are recruiting participants.[54]

> "As we are able to follow people with AD in the large population-based registries in Sweden, having a correct diagnosis allows us to carry out research to better understand the disease. This is all-too often overlooked'."
> **Maria Teresa Ferretti, Women's Brain Project**

The AD data landscape remains fragmented in most countries. Data consolidation is a large gap, with countries struggling to establish or develop systems to collect data across the care pathway (diagnosis, treatment, management). Regional variations, lack of coordination between levels of government, and absence of accurate standards make it challenging to gather a clear disease snapshot in each country. To address this gap, several countries are undertaking efforts to help streamline data collection related to AD and other dementias. This is the case in Sweden with the SveDem being used to collect and provide access to national dementia data while aiming to improve data robustness and breadth.[33]

Setting-up a European AD registry allowing for a standardised set of statistics would be instrumental for each country to regularly report on an epidemiological surveillance of AD.

Dementia plans

Most of the existing national dementia plans have a segment devoted to diagnosis, but few include a specific target for diagnosis rates or collect information about the number of newly diagnosed people with dementia.[24] National dementia plans, when existing, still do not adequately address the early detection and timely diagnosis of AD and tend to place more focus on support after a diagnosis is made.

To match the current innovation context, future dementia plans that will be developed at national level will need to include provisions for the early detection and diagnosis of AD. To make this possible, awareness-raising efforts about the value of innovation in this respect actively supported by those directly concerned (people living with AD, their families and healthcare professionals) will be instrumental in making this possible.

Dementia strategies must also be flexible and include a mechanism allowing the additions of new provisions or taking stock of new evidence discovered. In the Czech Republic, there is a regular monitoring of the implementation of the plan with a ministerial stakeholder platform. This is pivotal to ensure scientific discovery brings meaningful impacts to people living with ADs and the adaptation of the health systems to also strategically prepare for this innovation and integration of new interventions.

Securing full funding for the implementation of national plans remains a challenge in many countries. Countries must move beyond developing plans to securing funding for implementation.[33]

Adequate funding and monitoring of the plans' implementation is all too often lacking.

The Italian case[55]

In 2014, the Italian Ministry of Health launched the country's first National Dementia Plan: 'Strategies for the promotion and improvement of the quality and appropriateness of care interventions in the dementia sector'. The main purpose of the strategy was to promote and improve interventions in the field of dementia, including around specialist and therapeutic interventions, as well as focusing on the support of people living with ADs and families throughout pathway of care. Due to a lack of budget allocation, the strategy's objectives were unable to be translated into concrete actions. In 2020, the Italian government announced that funding for the strategy had been approved for 2021: € 15 million over a 3-year period. The primary objective is to finance social policies in the strategy and make investments in regional healthcare infrastructure to increase early diagnosis and improve monitoring and treatment for those living with dementia. While the allocated budget is not entirely sufficient, it represents a step forward in national efforts.

> "National dementia plans have been the vehicle for real changes that have mattered in the lives of those living with AD. I would urge every country in the EU to have an action plan that specifically focuses on diagnosis as the entry point to care and on research to be included in the care pathway. These should not be two separate streams."
> **Kristian Steen Frederiksen, European Academy of Neurolog**

Towards a more coordinated care management approach

Some international experimental studies have shown that a more coordinated care management approach that provides intensive dementia specific services in primary care produces the most promising results.[26] An example of an innovation in this field is the creation of interdisciplinary memory clinics within primary care settings. The emerging evidence points to the potential benefits of these programs in building capacity within primary care, while improving the efficacy of the use of specialist expertise. More research is needed to evaluate cost-effectiveness, feasibility and long-term sustainability of these innovations, and to test their replicability in primary care practices.[26]

Besides GPs, other professionals will have a role in identifying individuals with MCI or presenting with physical abnormalities that may suggests a suspicion of AD: such as, community nurses, diabetologists, cardiologists, ophthalmologists. In the Czech Republic, for instance, pharmacies are increasingly engaged in the diagnostic process. People are used to going to pharmacies and often feel more comfortable and less stressed than in a doctor's practice. Pharmacists are effectively used to communicate with the ageing population. Additionally, in the Czech Republic, ČALS (the Czech national Alzheimer's association) provides free testing and advertises this service through annual media and radio campaigns. Many people who believe that their GP's test was inaccurate, or that their GP did not investigate further often seek out this free testing.

**Identifying people living with AD in the community
The example of MOPEAD[56]
(Models of Patient Engagement for Alzheimer's Disease)**

Looking at innovative ways to uncover hidden prodromal and mild AD dementia cases, and to raise awareness both in the general public and among health professionals about the importance of early diagnosis, Models of Patients Engagement for Alzheimer's Disease (MOEAD), a IMI-EFPIA funded project) evaluated 4 detection and diagnosis strategies in five countries (Germany, the Netherlands, Slovenia, Spain, and Sweden): a web-based (WB) pre-screening tool, an open house initiative (OHI), a primary care–based protocol for early detection of cognitive decline (PC), and a tertiary care–based pre-screening at diabetologist clinics (DC). A subset of positively pre-screened patients of each strategy was offered referral to memory clinics for a full diagnostic evaluation, including a medical examination, blood tests, neuropsychological testing, magnetic resonance imaging and optional cerebrospinal fluid analyses.

The individuals pre-screened in the WB initiative were the youngest (mean = 70.1 years, followed by those pre-screened in the OHI (mean = 72.7 years), PC and DC initiatives (mean ages of 74.0 years and 73.3 years respectively).

A total of 2,847 individuals were pre-screened in one of these initiatives. More than half of these patients completed the WB pre-screening (52%) followed by OHI, PC, and DC. Overall, 39.7% of all pre-screened individuals had a positive result. Among them, evidence of advanced dementia was seen in the OHI followed by the PC and DC initiatives. The proportion of individuals with a positive result was higher among patients undergoing DC and PC pre-screening (58.3% and 44.4%, respectively) and lower among participants of the OHI (35.6%) and WB initiatives (36.8%).

The profile of patients with a positive pre-screening result differs between the four initiatives and there were differences between the countries.

The ability of each strategy to capture specific target populations makes them quite complementary.

**Promising coordinated care management
incorporates a combination of key strategies[29]**

- Use of multidisciplinary teams of clinicians with relevant expertise (as opposed to the traditional models of primary medical care in which the primary care practitioner takes the full responsibility for patient care);

- On-going care management, typically coordinated by a nurse working closely with the person with dementia/caregiver, attending a primary care practitioner, and other care providers;

- Provision of formal dementia training for primary care practitioners (and other clinic staff), including access to an advanced practice geriatric nurse and/or a medical specialist for educational detailing and consultation;

- Use of standard tools, protocols, and guidelines to ensure active case finding and consistent care processes;

- Access to various types of information technology resources (e.g., electronic patient records, medical record prompts, decision support tools, and Internet-based care management systems);

- Provision of education and support for persons with dementia/caregivers in collaboration with community agencies, such as local Alzheimer's Societies;

- Regular people living with AD follow-ups to monitor care processes and outcomes.

Consensus on real-world application of innovation

More research needs to be done on the real-world application of innovation. While an accessible, early, accurate diagnosis provides value in its own right, achieving consensus on the widespread and real-world application of BBBs is pressing in light of emerging DMTs. Opportunities for action and collaboration call for the emerging detection and diagnosis modalities to be sufficiently robust; a compelling framework for reimbursement and rational, equitable access, accounting for both the value of accurate diagnosis today and when expected DMTs are more readily available, and the through the identification and sharing of real-world lessons and best practices to accelerate use in clinical practice.[46]

The International Working Group on the clinical diagnosis of AD has proposed recommendations for how biomarkers should and should not be used for diagnosing AD in a clinical setting. They have, in particular, made recommendations for the use in clinical practice of blood biomarkers for amyloid β and tau pathology.[57] Their recommendations meet the project's workshops experts' views that blood biomarkers require further standardisation and validation before they can be broadly regarded as secure evidence of AD pathology.[57]

Importance of communication

Disclosing biomarker results and the related risk profile to people living with ADs should be seen as different from the disclosure of disease diagnosis. Within the lay community, AD is among the most feared diseases, given its outcomes. There is a big difference in the use and understanding of the term: for physicians, AD equates with neuropathological changes, whereas for people living with ADs, AD equates to dementia, dependency, and death. In the future, being said to be at-risk for progression, instead of in the preclinical stage of AD, might help in discussions with people living with AD regarding the risk–benefit balance regarding a putative treatment and its side-effects.[69]

The European Academy of Neurology and the European Alzheimer's Disease Consortium have issued a position statement on diagnostic disclosure, biomarker counselling, and management of people with MCI.[58] Alzheimer Europe has published a Position Paper on the disclosure of diagnosis.[59] A European consensus for the diagnosis of MCI and mild dementia is in its preparatory phase.[60]

The development of advanced diagnostic and treatment approaches for AD is at an early stage. Where it is believed that a therapeutic intervention could potentially halt or slow disease progression, this project has helped to compel the motivation to rethink the way society detects, diagnoses and treats the disease. The burden of the disease on societies at large and individuals calls for the development of impactful strategies for the healthcare systems, and people with dementia and their families or caretakers need to be better equipped to benefit swiftly from innovation.

☐ ACKNOWLEDGMENTS

☐ EXPERTS' BIOGRAPHIES

We would like to express our great appreciation to the experts for their valuable and constructive input during the development of this project.

Marco Blom
**Scientific Director, Alzheimer Nederland
(Alzheimer's Society in the Netherlands)**

Marco Blom (1961) is the Scientific Director of Alzheimer Nederland (Alzheimer's Society in the Netherlands). He is psychogerontologist and since 1987 involved in organisations and projects on dementia. He started his career at a Community Mental Health Centre in The Hague and in 1991 was appointed at the National Institute of Care and Welfare (now called Vilans) in Utrecht. In March 1997 he joined Alzheimer Nederland. He was involved in the development of the Alzheimer Cafes, the academic Alzheimer Research Centres and the online platform (www.dementie.nl) for people with dementia and their family caregivers. He was board member of the Delta Plan Dementia, the national program on dementia in the Netherland (2013 – 2020). In 2021 he was invited to chair a mission team on the topic of dementia within the Topsector Life Sciences and Health. Other affiliations: member of the editorial board of the Netherlands Journal of Psychogeriatrics (called Denkbeeld) and board member of Alzheimer Europe (since 2018).

Hana Marie Broulíková
Health Economist, Vrije Universiteit Amsterdam

Hana Marie Broulikova, PhD is a health economist specializing in mental health and dementia. She is an assistant professor at the Department of Health Sciences, Vrije Universiteit Amsterdam. She was responsible for the development of the National Dementia Strategy at the Ministry of Health of the Czech Republic. Currently, she advises the ministry on its implementation.

In her research, Dr. Broulikova investigates the effect of timely dementia diagnosis on care utilization and costs using nationwide healthcare registers. She specifically focuses on the question whether early interventions may reduce also health problems and healthcare utilization that tend to be primarily attributed to other diseases.

She continues collaborating with the Department of Public Mental Health, National Institute of Mental Health, where she previously worked on an evaluation of the ongoing reform of mental health care in Czechia. She was awarded a Fulbright Scholarship for a research stay at the Mailman School of Public Health, Columbia University as well as prizes by the Czech Alzheimer Foundation and the Czech Demographic Society.

Maria Teresa Ferretti
Scientific Director, Women's Brain Project

Maria Teresa Ferretti is a neuroscientist and neuroimmunologist, an expert in Alzheimer's and gender medicine. In 2016, she co-founded the non-profit organization «Women 's Brain Project» (of which she is currently Scientific Director), a world leader in the field of the study of sex and gender specificities and the importance of precision in neurological and psychiatric diseases.

She graduated in Pharmaceutical Chemistry and Technologies at the University of Cagliari (Italy), then studied and worked in England, Canada (where she earned a PhD in Pharmacology and Pharmacological Therapy at McGill University in Montreal), Switzerland and Austria. Her articles have been published in numerous journals, including Nature and PNAS, and she is regularly invited by major scientific conferences to lecture on Alzheimer's disease, precision medicine and the differences between men and women in neurology and psychiatry.

She has taught in numerous university courses and is currently a lecturer in the 'Certificate for Advanced Studies in gender medicine' course at the University of Zurich and 'External Teacher' at the Medical University of Vienna; in addition, she is responsible for continuous medical education modules for doctors and health professionals in the field of gender and precision medicine.

Passionate about scientific dissemination and animated by the desire to break the taboo on mental and brain diseases, she was a TED-x speaker in 2019 and 2021. She wrote in 2021, 'A headless girl' together with Antonella Santuccione Chadha, and in 2022 'Alzheimer Revolution', books that explain the complexity of brain disorders to the lay public.

Wiesje van der Flier
Scientific Director, Alzheimer center Amsterdam

Wiesje van der Flier (1975) is full professor and Scientific Director of the Alzheimer Center Amsterdam at Amsterdam UMC, in the Netherlands, where she works since 2004. She studied neuropsychology at the University of Utrecht. In addition, she is clinical epidemiologist. She leads the Amsterdam Dementia Cohort, an ongoing memory-clinic based cohort including over 6000 patients with deep phenotyping (MRI, EEG, CSF biomarkers,and PET) and linked biobank (blood, DNA, CSF). The Amsterdam Dementia Cohort is at the basis of many of the studies performed at the Alzheimer Center Amsterdam. Van der Flier has been (co)promotor of >20 theses and is currently supervising ~10 PhD projects. Van der Fliers main research areas are looking for the origin of AD, diagnosis & prognosis, and intervention & prevention. Van der Flier leads ABOARD (A Personalized Medicine Approach for Alzheimer's Disease), a Dutch public-private partnership of than 30 partners. Together with colleague Philip Scheltens, she has written a book, het Alzheimermysterie, which was published by the Arbeiderspers.

Kristian Steen Frederiksen

Co-chair, EAN Scientific Panel Dementia and Cognitive Disorders

Dr Kristian Steen Frederiksen is a consultant neurologist and Director of the Clinical Trial Unit at the Danish Dementia Research Centre, Rigshospitalet. Dr Frederiksen conducts research on a number of topics related to Alzheimer´s disease and Lewy Body Dementia including development biomarkers for the early diagnosis of dementia disorders and the clinical application of biomarkers. Dr Frederiksen also co-chairs the European Academy of Neurology Scientific Panel on Dementia and cognitive disorders.

Giovanni B. Frisoni

Full Professor of Clinical Neuroscience, University of Geneva

Clinical neurologist, Full Professor of Clinical Neuroscience at the University of Geneva, Switzerland, and Director of the Memory Clinic of the Geneva University Hospital. Former Scientific Director at the National Alzheimer's Centre in Brescia, Italy. Author of over 700 scientific papers listed in PubMed, imaging editor for Neurobiology of Aging, and founding editorial board member of The Lancet Neurology. Has led national and international projects funded by the European Commission, IMI, the Alzheimer's Association, Italian and Swiss Ministry of Health, and industry. Chairman of Alzheimer's Imaging Consortium at International Conference on Alzheimer's Disease in 2010 and 2011. Honorary member of the Austrian Neurological Society and of the French Society of Neurology, he has received the Investigator Award Winner of European Academy of Neurology in 2016.

Lutz Froelich

Head of the Department of Geriatric Psychiatry, Central Institute for Mental Health

Lutz Froelich is Head of the Department of Geriatric Psychiatry, Central Institute for Mental Health, Mannheim, Germany. He received his MD degree from Heidelberg University and is board certified Psychiatrist/Psychotherapist. In 1998, he became Assistant Professor for Psychiatry and Psychotherapy at Frankfurt University and in 2003, Professor of Geriatric Psychiatry at Heidelberg University, Germany.

His research had focused on the pathophysiology of Alzheimer's disease through animal models (Heidelberg University) and post-mortem human brain tissue (Würzburg University). His current research is on clinical dementia research, e.g. the role of biomarkers, clinical management of dementia and clinical trials in Alzheimer's disease.

He is member of the National and International Guideline Committees, and Chair of the European Alzheimer's Disease Consortium (EADC). He also is Deputy Chair of the Ethics Committee of the Medical Faculty Mannheim, University of Heidelberg.

Oskar Hansson

Full Professor of neurology, Lund University

Dr. Oskar Hansson gained his PhD in neurobiology in 2001 and his M.D. in 2005. He became senior consultant in neurology in 2012 at Skåne University Hospital, and full professor of neurology in 2017 at Lund University, Sweden. Oskar Hansson performs internationally recognized clinical and translational research focusing on the early phases of Alzheimer's and Parkinson's diseases. His work on biomarkers has led to over 350 original peer-reviewed publications. He heads the prospective and longitudinal Swedish BioFINDER studies (www.biofinder.se), where the research team focuses on the development of optimized diagnostic algorithms for early diagnosis, and also studies the consequences of different brain pathologies on cognitive, neurologic and psychiatric symptoms in healthy individuals and patients with dementia and parkinsonian disorders. Recently, the BioFINDER team has shown that Tau PET imaging can reliably distinguish Alzheimer's from other neurodegenerative diseases (JAMA, 2018) and to detect different subtypes of Alzheimer's (Nature Medicine 2021), and the team has validated blood-based biomarkers for early detection of Alzheimer's disease (Nature Medicine, 2020; JAMA, 2020, Nature Aging 2021, Nature Medicine 2021). He is the Co-Director of the strategic research area of neuroscience at Lund University, and responsible for research at the Memory Clinic at Skåne University Hospital.

Linus Jönsson

Professor of health economics, Karolinska Institute

Dr Linus Jönsson is Associate Professor of health economics at the Karolinska Institute in Sweden. His research focuses on economic evaluation of diagnostic technologies and treatments for Alzheimer's disease (AD) and other neurodegenerative disorders. Dr Jönsson has authored of over 100 original publications, reviews and book chapters, he serves on the Swedish government gerontology research council and has acted as scientific advisor to the National Board on Health and Welfare. He is coordinator for national and European research collaborations developing methods for assessing the value of new technologies to diagnose, treat and prevent AD (JPND-ADDITION, PREDEM). He co-chairs the International Pharmacoeconomic Collaboration on Alzheimer's Disease (IPECAD), and teaches health economics, outcomes research and decision analysis at the Stockholm School of Economics and Copenhagen University.

Lenka Krajčovičová
Assistant Professor, Masaryk University

Lenka Krajčovičová has a PhD in neurology at Masaryk University in Brno (Czech Republic). Her scientific topics include neurodegenerative disorders – Parkinson´s disease and Alzheimer´s disease in particular, movement disorders, cognitive disorders.

She has been involved in numerous research projects such as Microbiome in neurodegenerative diseases with cognitive impairment (Czech national recovery program), Diagnostics of Lewy body diseases in the prodromal stage based on multimodal data analysis, supported by Ministry of Health of the Czech Republic, Modulation of cognition and brain connectivity by noninvasive brain stimulation in patients with mild cognitive impairment due to Alzheimer's disease, supported by Ministry of Health of the Czech Republic, Effect of intensive dance-exercise intervention on cognitive function and changes of brain plasticity in healthy seniors and patients with mild cognitive impairment in early stage of Alzheimer´s disease, supported by Ministry of Health of the Czech Republic and Pre-clinical genotype-phenotype predictors of Alzheimer´s disease and other dementia (APGeM), supported by EU Joint Program – Neurodegenerative Disease Research.

Lenka Krajčovičová is a member of the Czech medical society, the Czech neurological society, the Section of cognitive neurology, the Section of extrapyramidal neurology and the Czech society for clinical neurophysiology.

Lucilla Parnetti
Full Professor of Neurology, University of Perugia

Lucilla Parnetti is the Director of Section of Neurology-Lab of Clinical Neurochemistry and Post-Graduated School of Neurology, Dept of Medicine and Surgery at the University of Perugia. Her main expertise is in the field of CSF biomarkers for early diagnosis of neurodegenerative diseases. In the last two decades, her scientific interest has been focused on the early-stage, preclinical and differential diagnosis of Alzheimer's and Parkinson's disease through immune-enzymatic, fluorimetricand biophysical assays.

Helen Rochford-Brennan
Vice Chair, Irish Dementia Working Group

Helen Rochford-Brennan is a Global Dementia Ambassador, former Chair, and currently Vice Chair, of the Irish Dementia Working Group; and currently a member, (formerly Chairperson), of the European Working Group of People with Dementia and its nominee to the Board of Alzheimer Europe.

Helen sits on the Monitoring Committee of Ireland's first National Dementia Strategy and is a panel member of multiple advisory groups in Ireland and Europe.

Throughout Helen's time with these organisations, she has campaigned to raise awareness of dementia through a rights-based approach, including through the media, speaking at international conferences, engaging with pharmaceutical companies, scientists, clinicians, educators, students and through participation on various research projects, including those focusing on developing evidence-based diagnosis, palliative care, rural isolation and, more recently, living during the COVID-19 lockdown. Helen strongly believes in the primacy of Public-Patient Involvement. She has contributed to several books and documentaries about dementia, and has received several awards for her advocacy work, including an Honorary Doctor of Laws degree from the National University of Ireland Galway for her work on the Rights of People with Dementia.

Philip Scheltens
Head Dementia Fund, EQT Life Sciences

Prof. Dr. Philip Scheltens studied at the VU University Amsterdam, Netherlands, gaining his MD in 1984, and PhD in 1993. He became Professor of Cognitive Neurology and founder of the Alzheimer Center at Amsterdam University Medical Centers in 2000, which he directed until 2022. Currently he devotes most of time heading the Dementia Fund at EQT Life Sciences, that he started in 2020.

He has been the (inter)national PI for over 35 studies, including phase 1-3 multi-center clinical trials. He supervised >75 PhD theses since 2000. He founded the Dutch national plan against dementia and served as chair of the board. He is co-editor-in-chief of Alzheimer's Research & Therapy and co-leads various EU projects. He authored over 1100 peer reviewed papers and > 75 book chapters and co-edited several major text books.

He is member of the Royal Dutch Academy of Arts and Sciences (KNAW) since 2011. In 2016 he was awarded the European Grand Prix for Alzheimer's Research. In 2020 he was Knighted in the Order of the Netherlands Lion by the King of the Netherlands. In 2021 he was elected honorary member of the European Academy of Neurology and was appointed chair of the World Dementia Council.

Charlotte Teunissen
Professor in Neurochemistry, Chair of the Neurochemistry lab, Amsterdam UMC

Charlotte Teunissen (full professor in Neurochemistry) aims to improve care of patients with neurological diseases by developing body fluid biomarkers for diagnosis, stratification, prognosis and monitoring treatment responses. Studies of her research group span the entire spectrum of biomarker development, starting with biomarker identification, followed by assay development and validation, and extensive clinical validation to ultimately implement novel biomarkers in clinical practice.

She is responsible for the Alzheimer Center Amsterdam body fluid and leads several international biomarker networks, such as the CSF Society and the Alzheimer Association-Global Biomarker Standardization consortium, and the recently founded Coral proteomics consortium. She is the coordinator of the Marie Curie MIRIADE project, aiming to train 15 novel researchers into accelerate dementia biomarker development.

Saskia Weiß
Managing Director, German Alzheimer's Association

Saskia Weiß works as Managing Director of the German Alzheimer's Association. Personal experiences with dementia in her family brought her in contact with the Alzheimer Association Berlin in 2004 and the desire to complete an internship there during her studies. In addition to her private experiences, she has always been professionally connected to the topic of dementia. In 2008 she started to work as a social worker for the German Alzheimer's Associations.

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European Brain Council

Rue d'Egmont, 11

BE-1000 Brussels

Belgium

Tel: + 32 (0) 2 513 27 57

info@braincouncil.eu

@EU_Brain

European Brain Council

European Brain Council

braincouncil.eu

European Federation of Pharmaceutical Industries and Associations

Leopold Plaza Building

Rue du Trone 108

B-1050 Brussels

Belgium

Tel: +32 (0)2 626 25 55

reception@efpia.eu

@EFPIA

EFPIA - European Federation of Pharmaceutical Industries and Associations

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efpia.eu