



Ministry of Health, Welfare and Sport

Defeating dementia

ESSAYS
volume 2

*Working together for health,
wellbeing and resilience*



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Foreword

Joanne Pike

I am delighted to introduce this collection of dementia essays led by the Netherlands' Ministry of Health, Welfare and Sport. The essays are being published in coordination with the Alzheimer's Association's International Conference (AAIC) in Amsterdam, and feature experts from around the world, examining efforts in prevention, emerging treatments, clinical trials, diagnosis and care. While all important individual topics and perspectives, there is a significant and common theme that runs through them all. Hope.

When treatments become available for diseases, everything changes. It has been more than 100 years since Alzheimer's was first identified as a disease. Now for the first time we have treatments to change the underlying course of Alzheimer's. Our community deserves a moment to celebrate this milestone and the dedication required to realize it. While we know the treatments currently available do not halt the disease, they do give people in the early stage of Alzheimer's disease more time to maintain their independence and enjoy their family, their friends and their lives. The importance of this time cannot be overstated.

There are many more therapeutics in the pipeline which strongly suggests that the years ahead will bring additional treatments. These treatments will build on the progress we've made today, targeting the disease from a variety of angles. This progress is an unstoppable tide and will benefit millions living with Alzheimer's disease now and in the future.

We know there is still much for us to accomplish together. AAIC, the world's largest gathering of dementia researchers, thought-leaders and policymakers, showcases this forward momentum. AAIC will feature exciting scientific progress, including the latest understanding of the underlying mechanisms of disease, identification of new biomarkers and establishment of new drug targets. The Alzheimer's Association is proud to have funded research in these areas and nurtured the careers of many scientists. That commitment will continue.

Science is delivering treatment options, and now our policy makers and health systems must deliver too. The availability of treatments impact all the themes featured in these essays and will change the practice of prevention, diagnosis and

care. But that only happens if people with Alzheimer's have access to effective diagnosis and treatment options in a manner that is culturally appropriate for them. We cannot let this moment of hope turn into one of frustration. Individuals who need and would benefit from treatments must be able to access them. The Alzheimer's Association will be relentless in demanding that, and I know you will be too.

On behalf of the Alzheimer's Association I welcome this initiative from the Government of Netherlands to share perspectives from leaders in our field. The publication of these essays will serve as a precursor to the meeting planned for October that will build upon important discussions at the G7 Health Ministerial meeting on dementia that took place in Nagasaki, Japan this past May. These discussions highlight the need for governments in high-income countries — as well as in low and middle income countries — to embrace progress made in diagnostics and treatments, and take action. People with dementia and their families around the world are counting on them and on all of us.

JOANNE PIKE, DrPH, President and CEO Alzheimer's Association®, Alzheimer's Impact Movement (AIM)

Joanne Pike, DrPH, is president and CEO of the Alzheimer's Association, the global leader in Alzheimer's and dementia care, support and research. With her progressive experience in social support and public health, she is leading the organization during a transformational period. Novel treatments for people living with Alzheimer's are emerging, and equitable access — as well as reaching all those affected with education and support — has never been more important. Since joining the Alzheimer's Association in 2016, Dr. Pike has held several roles, highlighting her increasing leadership within the organization and the cause. As chief programs officer, she was responsible for overseeing care and support services offered to all those affected by the disease; outreach aimed at creating partnerships with health systems, physicians and other health care professionals; long-term care initiatives focused on person-centered care delivery models; and growth strategies to reach more individuals through quality improvement, education, and support



programs and services. From 2020 to 2021, she served as chief strategy officer, directing the implementation of the strategic plan throughout all elements of the organization. In November 2021, Dr. Pike was named president, and in this role, guided the Association's efforts to accelerate research; enhance care and support; advance public policy; strengthen diversity, equity and inclusion; increase concern and awareness; and grow revenue.

Dr. Pike is also the president and CEO of the Alzheimer's Impact Movement (AIM), a separately incorporated advocacy affiliate working to advance and develop policies to overcome the disease.

During her 25 years in public health, Dr. Pike developed and executed health-focused initiatives while implementing revenue strategies to support those measures. She has successfully leveraged public and system policy to advance public health outcomes with a particular emphasis on outreach to underrepresented and underserved communities. Prior to joining the Association, Dr. Pike spent 13 years in leadership positions at the American Cancer Society and three years as executive director of the Preventive Health Partnership, a collaboration among the American Cancer Society, the American Diabetes Association and the American Heart Association aimed at preventing cancer, diabetes, heart disease and stroke. Dr. Pike holds a doctorate in public health leadership focused on health policy and management from the University of North Carolina at Chapel Hill.

The Next Frontier Against Dementia: Four Guidelines for Public Health Action on Brain Health

Matthew Baumgart

Over the last 40 years, the fight against Alzheimer's and other dementias has involved addressing better medical care and promoting early detection and diagnosis. It has sought to improve social care and expand assistance and support for caregivers. It has been a quest for treatments – and the research dollars needed to develop them. While we have seen historic progress in this fight, many battles still remain. And it is now time to enter a new frontier in the fight: a public health strategy to address brain health and reduce the risk for cognitive decline and dementia.

During the early stages of the COVID-19 pandemic, public health officials often spoke about the need to “flatten the curve” of cases to help avoid overwhelming the health care system. We are now facing the prospect of an extremely steep curve of dementia cases. Projections estimate 139 million people worldwide will have dementia in 2050, nearly triple the number of current cases. This steep curve threatens to overwhelm the health and social care systems unless we can do something about it – unless we can flatten the curve by preventing people from developing dementia in the first place or delaying the point at which they develop it.

Prevention takes time, especially with respect to late-life chronic conditions like dementia. If we are going to change the dementia curve in the future, the work must begin in the present. We must enter a new frontier of dementia prevention. As we begin this public health effort, we would do well to be guided by the following observations.

Don't let clinical evidence be the enemy of the population's health.

Clinical-level evidence from randomized controlled trials is the gold standard in scientific knowledge and proof. Unfortunately, the clinical-level evidence on modifiable risk factors for dementia is not yet sufficient to indicate how any individual can prevent dementia. Meaning, the science is not

yet at the point where a doctor can confidently tell a patient, “Do this one thing and you can prevent dementia.” There is a less-than-ideal level of clinical evidence, but it should not govern public health action. Population-level evidence on modifiable risk factors tells a different story. Sufficiently strong observational and epidemiological studies show that if you can reduce the prevalence of certain risk factors in the population, you can improve the brain health of the population, reduce cognitive decline, and possibly reduce the number of dementia cases in the future. This is what should guide public health action. Indeed, the evidence is strong enough that public health agencies have a responsibility to help educate everyone about what the science concludes: that certain healthy behaviors are good for your brain health.

Avoid the shiny objects.

The modifiable risk factors with the strongest evidence are not easy to tackle. It is hard to get people to exercise, change their diet, prevent diabetes and obesity, quit smoking, or control hypertension. The difficulty in changing behaviors, combined with the ever-evolving understanding of the science about modifiable dementia risk, can result in a tendency to latch onto the easy, shiny object that is the subject of the latest news report. For example, “Just eat blueberries and you can prevent dementia,” or “Read a book every day and your problem is solved.” The seemingly easy solution is unlikely to be the complete solution, or the solution at all. At the same time, we cannot let skepticism about the shiny objects derail action. There is evidence for modifiable risk factors that can make a difference, gleaned from numerous studies over a long period of time. While we should not glom onto the latest fad, we also cannot let the uncertainty caused by fads delay public health action. Avoid the noise, stick with the signals.

Shift our mindset.

For decades, those working to provide care, support, and assistance to individuals with dementia have talked to and worked with older adults – because dementia is overwhelmingly a condition of older age. When we have worked with those under the age of 65, it has been primarily family members of those living with dementia or the relatively small proportion of individuals with younger-onset dementia. This mindset of focusing only on older adults will hamper dementia prevention efforts. Many health conditions and behaviors in middle age or younger can have an effect on later-life risk of dementia. Educating older adults about early detection and diagnosis is a good focus; educating *only* older adults about brain health and risk reduction is not sufficient

and will significantly hinder success. We need to educate people about risk reduction before they reach older age. We need to talk to people not just when they need our help, but before they need our help – in the hope that they will never need our help.

It's not just about the individual.

Everyone can, and should, take personal responsibility for improving their own health. Encouraging individuals to change behaviors that are bad for brain health and engage in behaviors that are good for brain health must be a public health focus. But individual responsibility can only go so far. For example, you cannot address diet among people who live in food deserts. You can tell them to eat healthy foods, but if they do not have access to a store that sells those healthy foods, your message is in vain. Similarly, you can encourage physical activity and exercise, but if people live in unsafe neighborhoods, do not have access to open spaces, or cannot afford a gym membership, their ability to take action is limited. The point is, individually-modifiable risk factors are not always fully modifiable by an individual. Environments can hinder efforts to adhere to a brain healthy lifestyle. As a consequence, successfully improving brain health in the population means addressing both individual behavior *and* the environments in which individuals live, work, and play.

This can be done. This must be done. The next frontier awaits.

**Matthew Baumgart, Senior Director of Public Policy
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Matthew Baumgart is Vice President of Health Policy for the U.S. Alzheimer's Association, leading a range of projects at the intersection of policy and programs to achieve an aggressive agenda that serves all those affected by the disease. In this role, he heads the Public Health Center of Excellence on Dementia Risk Reduction, funded by the Centers for Disease Control and Prevention. In addition, Baumgart directs the Association's global public policy efforts, working in collaboration with Alzheimer's Disease International, the World Dementia Council, and the World Health Organization. Baumgart joined the Alzheimer's Association in 2009 and has served in roles overseeing policy development, public health policy initiatives, federal affairs, and state governmental affairs. Prior to joining the Association, Baumgart spent nearly 20 years working in the United States Senate, including as legislative director for Senator Barbara Boxer of California and legislative assistant for over a decade to Senator Joe Biden. Baumgart has a degree in communications with a second major in political science from Washington State University.



Strategies and interventions to bring brain health policy alive

Agustin Ibanez, Stefania Ilinca & Brian Lawlor

The value of brain health as a concept and an approach

Brain health is about achieving the optimum state of cognitive, sensorimotor, social-emotional, and behavioural functioning across the life course (WHO, 2022; Chen et al. 2021). Brain health is therefore more than the absence of brain disease: it refers to optimizing and protecting brain function at each stage during the life course, so that individuals can reach their full potential in terms of mental and physical health, wellbeing and engagement in activities that matter to them. Brain health is a positive non-stigmatising value, like physical fitness, and should be promoted at societal and community levels because achieving better brain health improves wellbeing and quality of life for individuals, and fosters human and economic development (Lock, 2023). Compromised brain health and brain disorders carry a huge societal burden, estimated to reach as much as \$8.5 trillion globally in yearly productivity losses alone (Eyre et al., 2023).

Understanding brain health not as an absolute value in relation to a common standard but rather as a function of an individual's circumstances, abilities, and potential at any given life stage, significantly expands the scope for prevention and health promotion. Brain health can be promoted and maintained even in the presence of brain illnesses such as dementia. Rethinking dementia from the perspective of brain health is an important and hopeful narrative as it emphasises that even in the presence of disease, there are measures that can be taken to protect the brain, and potentially slow down or delay further decline, all of which may improve outcomes and quality of life for people living with dementia and their care partners.

As opposed to the traditional disease focused approach, reframing the discourse in terms of brain health holds the promise of added value for:

- Individuals – as it offers a more positive and coherent framework for guiding risk reduction and healthy behaviours at every stage of the life course;
- Public health – as it provides a framework for guiding prevention efforts across a range of diseases and can underpin more comprehensive health promotion efforts;
- Research and innovation – as it can focus more on opportunities for prevention, modifiable risk factors, resilience, cognitive reserve, blue populations, and protective factors;
- Treatment and care – as it can promote continuity and person-centeredness and an orientation towards care outcomes that are meaningful to individuals (quality of life, functional, independence, control) rather than standardized clinical outcomes;
- Health policies and care systems – as it can contribute to cost-effectiveness and system sustainability by lowering the burden of disease and associated treatment costs, and it offers clear targets for improving population health and wellbeing with benefits accumulating beyond the health sector.

Tackling modifiable risk factors

While there are several non-modifiable risks to brain health and the development of dementia (e.g., age, sex and genetic factors) many risk factors are modifiable or treatable. Notable in this category are high blood pressure, diabetes, head injury and concussion, age-related hearing loss, pollution, excess alcohol, smoking, lack of social connection, low education, low levels of physical exercise, poor sleep and depression (Livingston et al., 2020). A public health approach that promotes protective factors and mitigates risk factors across the life course, appropriately mixing population-wide and at-risk targeted interventions, is the best way to optimize brain health and prevent cognitive decline and dementia (Sabayan et al., 2023). Prediction modelling suggests that successful public health measures that lead to control of blood pressure, correction of hearing loss and stopping smoking has the potential to reduce dementia incidence. A modelled example of what can be achieved if we could successfully implement treatment of hypertension, brought about smoking cessation, and introduce hearing aids for those with age-related hearing loss, suggests that it would reduce dementia prevalence over time by 8.5% with cost savings of £1.862 billion annually in the UK and deliver significant improvements in quality of life (Mukadam et al. 2020). Similarly, in the USA, investment in Alzheimer's disease and dementia treatment is estimated to lead to cost savings of over \$360 billion up to 2030 (in direct and indirect costs of dementia), while a prevention-oriented approach is likely to accrue considerably higher cost savings, in the order of \$860 billion (Economist Group,

2022). Comparative estimates across several OECD countries confirm the higher potential of prevention approaches compared to treatment-oriented approaches, to avert direct and indirect costs for care systems and societies, especially through reduction of productivity losses.

Lessons learned from past experiences in the area of global public health can help chart a course forward. Efforts to address modifiable risk factors for heart disease have led to reduced deaths from heart attack and stroke, and although cardio-vascular diseases remain the leading cause of death globally, prevention efforts have been instrumental in decreasing deaths, disability and costs. Brain health can become the new heart health and should align with existing health promotion and prevention campaigns for cardio-vascular risk factors. Taking a similar prevention-oriented approach for brain health, there is enormous potential to reduce the number of people living and dying with dementia, especially if a focus on equity drives the design of global, national and local responses.

Social determinants of brain health

The exposure to risk over the life course and the effects of such exposure on health outcomes is intricately linked to a complex set of socio-demographic, environmental and economic factors. Better data collection and further research is needed to pinpoint the exact mechanisms (e.g. physiological, behavioural, or access and care pathways) and to understand how individual circumstances mediate the association between exposure to risk factors and declines in brain health. However, a robust evidence base indicates that gender, race and ethnicity, educational achievement, employment status and financial security can turn into many sources of intersecting disadvantage, placing some population groups in positions of extreme vulnerability with high exposure to risks and limited ability to mitigate that risk. While sustained action within health systems can help reduce population level risk, and address inequalities in risk exposure and timely access to care to some extent, successful policies to optimize brain health must rely on more comprehensive, cross-sectoral approaches that address the root causes of inequity, alter social contexts and transform the systems and structures that reinforce socio-economic disadvantage.

Key components of policy approaches to optimize brain health for all

In order to achieve equity, effectiveness and sustainability, future policies targeting brain health for all should prioritize three key components:

- a awareness and facilitating access to information for care professionals, individuals and communities;
- b re-aligning health and social investments to promote healthy lifestyles and behaviours, as well as person-centred care models;
- c addressing head-on, through whole-of-government and society-wide approaches, the structural factors that determine health and wellbeing.

Knowledge and awareness

A significant impediment to improving brain health is the knowledge and awareness gap that exists amongst both the general public and health and care professionals, who are largely unaware of the risks to brain health and what can be done about it. Therefore, improving brain health in the population must start with awareness raising and access to reliable, understandable and actionable information for the general public and for health and care professionals. If individuals understand why brain health is important, how it can be improved and how risks to brain health can be avoided and reduced, they are more likely to change their attitudes towards risky health behaviours and exposures, and to take appropriate actions to avoid them. This can be achieved through general health communication and education campaigns, leveraging the broad relevance of brain health for all population groups, in combination with targeted messaging for specific age and high-risk groups on recognizing and addressing the impact of upstream lifestyle, social and commercial determinants of brain health and cognitive decline in later life. Similarly, education and continuous professional development programs should provide health and care professionals with updated information on brain health, risk factors across the life course and how they can be addressed, as well as equip them with the skills to efficiently communicate with various stakeholders about brain health and related diseases.

There is always a danger that awareness and education programs will only reach the well-educated and those that are ready to change. Brain health is for all, and has most to offer to those at increased risk, for example those exposed to poverty or other forms of socio-economic disadvantage. For this reason, efforts must focus on ensuring that the impact of inequities on brain health and how they exaggerate the negative impact of risk factors are properly understood, and that the messaging and design of education interventions is adapted to the specific needs of vulnerable groups.

Lifestyle and behavioural factors

While improving knowledge and awareness about brain health is a necessary first step towards reducing risky health behaviours and enacting positive lifestyle changes, it is rarely sufficient on its own. Even when armed with the knowledge, achieving meaningful and lasting changes in health behaviours is challenging for most. Behaviour change for brain health requires sustained effort over long periods and is more likely to succeed when peer and professional supports are available. Evidence is building on the benefits of programs and interventions to promote healthier lifestyles and reduce exposure to risk factors relevant to brain health that can be delivered in primary care, community or digital settings. For example, digital technologies that can monitor risk indices and behaviours and provide a platform for intervention and connections, all of which could be positive for brain health. But openness to leverage the potential of new technologies must be complemented by actions to meaningfully change structural conditions that determine health behaviours. Creating community readiness, improving safety of public spaces, access to exercise and green spaces can complement and support individual efforts towards behavioural and lifestyle changes, making them more likely to succeed and be more sustainable, particularly in marginalised and vulnerable populations.

Structural factors and brain health

Policy-makers should consider how to successfully bridge across multiple sectors (e.g., health, education, social care, the environment), as brain health is strongly influenced upstream by many social and environmental determinants that can only be affected by large systems changes. Unfortunately, for a considerable proportion of the world's population, choices and opportunities to lead healthy lives are severely constrained by social, cultural and structural factors that are not under the control of individuals or local communities. As highlighted above, poverty, race, gender, ethnicity, migration status and other socio-demographic characteristics determine and restrict the decisions that are available to individuals. When healthier alternatives are unavailable, unaffordable or contradict social norms and expectations, it is not only challenging but can be nearly impossible for individuals to control exposure to brain health risks on their own, not matter how well motivated they might be. Whenever individual control over lifestyle and health choices is limited, it is both necessary and more effective to prioritize improvements in the systems, structures and environment around them. This is where government policy, that takes a population strategy to addressing risk factors can

be important but it must at the same time be accompanied by strategies that target inequalities and risk factors in those that are most vulnerable.

Charting a way forward

It is vital that we act now to prioritize brain health policy globally. This will require sustained investment in designing and promoting interventions and policy solutions that tackle head-on the many challenges at individual, health and care services and systems, as well as at the societal level. We identify 8 key challenges, and for each of them suggest promising levers for policy intervention, from a growing evidence base ([see Panel 1](#)). These levers can help guide policy-makers at local, national and global level, as well as inform the efforts of advocates, researchers, industry and community leaders.

Priority should be given to implementing early prevention strategies, continually nurturing our brain's plasticity, and broadening education to enhance understanding of modifiable risk factors. By taking proactive, multisectoral steps towards promoting brain health, we have the potential to significantly reduce the incidence of dementia, improve the brain health of all citizens, and contribute cost-effectively to our health and care systems. Furthermore, we must consider the social determinants of brain health and the role of policy in shaping our environment and environmental risks to brain health. This necessitates promoting and prioritizing cross-sectoral collaborations to address the root causes of inequity and risk exposure. Working collectively towards a future where brain health is prioritized at every stage of life can foster individual wellbeing, public health, the sustainability of health and care systems and equitable economic growth, marking a unique step forward. Our actions today can pave the way for healthier brains tomorrow.

Panel 1. Challenges and levers for policy intervention to bring brain health policy alive:

- 1. Feasibility and costs:** Implementing public health measures, developing education tools, creating brain health community hubs, and other strategies mentioned requires significant resources and time. The cost and logistical challenges of such comprehensive interventions can be prohibitive, particularly in resource-constrained settings, where they compete with and could risk crowding out investment in other public health areas. Policy Levers: Implement tiered and scalable approaches to public health interventions that are sensitive to local contexts. Prioritize actions based on available resources, aiming for comprehensive programs where possible, while ensuring at least basic, high-impact measures are implemented globally. Explore synergies and align where possible with existing public health initiatives (e.g. cardio-vascular health, mental health).
- 2. Cultural and socioeconomic differences:** Different cultures have various beliefs and attitudes towards health, which might affect the acceptability and feasibility of brain health strategies. Similarly, socioeconomic factors like poverty and lack of access to healthcare could hinder the effective execution of these strategies. Policy levers: Employ equity and cultural adaptation oriented approaches, by tailoring brain health strategies to respect cultural beliefs and socioeconomic realities. This is best achieved by ensuring user and local community engagement in every step of policy design, implementation and monitoring. Implement targeted interventions to reach the most vulnerable populations and establish cross-cultural education programs to raise awareness and acceptance of brain health.
- 3. Individual behaviour and motivation:** Changing individual behaviours and lifestyle choices, which are critical to promoting brain health, is often difficult and requires sustained motivation. The effectiveness of education and awareness programs depends largely on individual willingness to make changes. Moreover, in the case of vulnerable populations, these challenges are at least partially independent of individual decisions. Policy levers: Adopt a structural, population-based approach and apply behavioural insights to the design of policies and interventions and the functioning of health systems and communities. This approach emphasizes population-wide changes in environment and society that make healthier choices easier, rather than relying on individual change alone.
- 4. Evidence base:** It is important to have robust scientific evidence supporting any public health interventions and recommendations for brain health. While there is evidence suggesting that addressing modifiable risk factors can improve brain health and reduce dementia risk, more research is needed to determine the efficacy of specific interventions and approaches, especially in global and diverse settings. Policy levers: Invest in strengthening data infrastructure and comprehensive research to evaluate the effectiveness of various lifestyle interventions on brain health. Priority should be given to research that recognizes diversity, helps build the evidence base for under-prioritised issues and supports the development of feasible, equitable and sustainable solutions that take a global perspective.
- 5. Continuum of care:** While prevention is crucial, we need to value the importance of available services and supports across a continuum of care from prevention and health promotion, to curative, rehabilitative, assistive and palliative care. To equitably address the needs of those already living with cognitive decline or brain diseases, it is crucial to develop balanced approaches that include preventive, therapeutic and assistive measures. Policy levers: Recognize the importance of therapeutic and assistive strategies alongside preventive measures, ensuring balanced investment and allocation of resources. A brain health approach that encompasses treatment and care provides hope and gives agency to people living with dementia, to their care partners and families.
- 6. Intersectoral collaboration:** Achieving collaboration between health, education, social care, and the environment can be difficult due to bureaucratic hurdles, competing priorities, and resource allocation challenges. Further complexity is added by intricate governance structures at national, regional and local level and difficulties in coordinating investments and pooling resources across the public and private sectors. Policy levers: Promote brain health diplomacy, fostering a transdisciplinary approach that encourages collaboration across sectors, such as health, education, social care, and the environment. Invest in training and education to break down

bureaucratic barriers and align priorities across these sectors.

7. **Digital literacy and the digital divide:** Increasing reliance on digital technologies for monitoring and intervention in brain health could exclude those that lack access to such technologies or the skills to fully engage in a digitalized and virtual environment. These are often individuals from disadvantaged groups that could most benefit from cost-effective innovations in treatment and care. Policy levers: Develop inclusive digital policies and strategies to ensure digital health interventions are accessible to all, including the most disadvantaged groups, and that they help reduce rather than accentuate inequalities in health and access to care. This could involve public-private partnerships to provide necessary technologies or creating alternative, non-digital avenues for intervention. Invest in developing digital health literacy and skills in the population, with particular attention to up-skilling health and care workers in community-based settings, in remote, rural or disadvantaged areas.
8. **Tackling broader social determinants:** Addressing the real complexities and challenges of the social determinants of brain health require going beyond education and awareness. Fighting structural determinants of health, reducing poverty, and addressing social inequalities are all crucial for brain health. These are challenging issues that extend beyond the purview of health-focused interventions/education. Policy levers: Advocate for health policies that address broader social determinants of health and brain health, such as poverty, inequality, and education as well as the commercial and digital determinants of health. This should involve partnerships with non-health sectors and the private sector, advocating for policies that promote social equity and create healthy environments. At a global level, a transformation of economic systems will be required to ensure delivery on the values and outcomes that matter most to individuals and to societies. Stakeholders at all levels must actively monitor progress on the achievement of core societal values, leveraging private and public resources and intelligence through alignment of goals and shared accountability, and promote a focus on health outcomes in research, innovation and industrial development (WHO Council on the Economics of Health for All, 2023).

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The challenge of advancing dementia treatments and care in LMICs

Paola Barbarino

Every 3 seconds someone in the world develops dementia (Alzheimer's Disease International, 2015). Accordingly, at this moment in time, there are estimated to be over 55 million people living with the condition across the world, a figure set to rise to 78 million by 2030 and 139 million by 2050 (World Health Organization, 2021). Increased global longevity and a greater exposure to dementia risk factors across the life course is precipitating a global public health crisis, with evidence suggesting that more than two-thirds of those living with dementia are estimated to be living in low and middle-income countries (LMICs) (Siti Maisarah Mattap, 2022) and this number is rising (Alzheimer's Disease International, 2019).

Dementia is the 7th leading cause of death globally, and increasingly the leading cause of death in many countries (World Health Organization, 2021). There is also an economic argument for a public health response to dementia, with the condition expected to cost the global economy \$1.3 trillion USD per annum, a figure set to increase to 2.8 trillion by 2030 (World Health Organization, 2021). Globally, of these costs, 50% are attributed to informal care, 36% to long term care and 14% to direct medical costs; in LMICs, almost two-thirds of these costs are attributable to informal care (World Health Organization, 2021). Correlating with the aforementioned data, more people with dementia live at home in LMICs, in part as a consequence of less long-term care facilities (Anders Wimo, 2018). This results in a greater burden on informal carers, principally women who constitute 70% of carers for those living with dementia. Carers frequently are required to leave employment and study, impacting economic output. Furthermore, mounting evidence is suggesting that up to 40% of cases of dementia could be delayed or reduced by addressing just twelve modifiable risk factors (Gill Livingston, 2020). Accordingly, addressing arguably the greatest public health crisis of a generation, makes fiscal, social and moral sense.

Despite the human and economic burden that dementia presents to those living with dementia, carers and the

wider society, many governments remain reticent to act or acknowledge this growing public health crisis, evidenced in part by the lack of progress towards the targets of the Global Action Plan on the public health response to dementia, where no targets are on track to be met by 2025 (World Health Organization, 2023). Furthermore, stigma and inadequate understanding of the condition contribute to this apathy and inaction. 62% of health care practitioners still consider dementia to be a normal part of aging, with 1 in 4 of the general public believing there is nothing which can be done to prevent dementia (Alzheimer's Disease International, 2019). These misunderstandings are further compounded by stigma surrounding the condition, with some still believing the notion that dementia is witchcraft or that it relates to a weakness of character (Gauthier S, 2021). It is clear that if we are to address the growing public health crisis that dementia presents, there must be a concerted and robust collaborative global advocacy effort, both through governmental policy and through broader awareness campaigning.

Recognising the need for a global response to dementia, Alzheimer's Disease International (ADI) was founded in 1984 by representatives from Alzheimer's associations in the United States of America, the United Kingdom, Australia and Canada, joined by observers from Belgium, France and Germany. This small group determined that there was an immediate need to form an international organisation, to strengthen national Alzheimer's disease and dementia associations to advocate for those living with the condition. ADI has grown substantially over the past 39 years, bringing the membership to 105 full members with many more in development. While the membership has grown considerably over that time, the fundamental necessity to strengthen the ability of emerging and developing associations to advocate to their governments remains unchanged. More often than not, those organisations which require the most guidance and capacity building are those residing in LMICs, where often the need for an association which advocates for those living with dementia and carers is the greatest.

Capacity building is a resource and time intensive process. There have been several therapeutic and diagnostic advancements in the past few years. ADI and our associations are becoming increasingly concerned by the possibility of unequal access to emerging disease modifying therapies between affluent and economically disadvantaged nations. The requirement for a confirmatory diagnosis of Alzheimer's disease (including the associated required level of health system preparedness), expected to be imposed by most

payers, will undoubtedly be a barrier to accessibility to most persons living with Alzheimer's disease in LMICs. This, combined with the high list price, will all but preclude access to these treatments to all but the most affluent societies.

LMIC's are also facing a considerable threat to their healthcare provision in the form of health care practitioner migration. High income countries are increasingly finding themselves with a shortage of health care workers and are addressing this through encouraging the migration of skilled health care practitioners from LMICs. Increasingly, migration agreements and treaties for health care workers are being formalised by states in an effort to address shortages. While these agreements undoubtedly benefit HICs to address the shortages in the staffing of their healthcare systems, and may be advantageous to LMICs governments who see this as a way to receive support for health care initiatives and to provide further education to health care workers for their eventual return, this reciprocally has dramatic effects on the availability and strength of health care systems and services in the LMICs and HICs are often criticised for not adhering to these pledges.

As we find ourselves in an age where disease modifying therapies for Alzheimer's disease are increasingly becoming a reality rather than a hope, we as a global community must also transition to ensure equitable access to treatments and care to all those who can benefit from it. This includes placing greater value in research that includes LMICs populations and guarantees true diversity and inclusivity. There are many barriers to clinical trials and research being conducted at LMIC the level, but they are not insurmountable. This complexity often discourages industry and governments who must put a greater emphasis on resolving these issues and facilitate a process that eventually will benefit its citizens. Similarly, industry would have to persevere and not halt at the first signs of red tape or complexity. We at ADI believe that we are on the cusp of great and positive changes in our cause but there needs to be a collective and concerted effort to ensure everybody can benefit from these important advances and this requires coordination, good will and compassion at multilateral level.

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Paola is CEO of ADI. Prior to this, she was CEO of LIFE and occupied senior positions with Cass Business School, Tate, British Library and IIED. Previously she was a NonExecutive Director of the Non-Communicable Disease Alliance (NCDA), a Trustee of Shelter, the housing/homelessness charity, and of MLA London. She holds a degree cum laude in Classics from Federico II Napoli University, an MA in Field and Analytical Techniques in Archaeology and an MA in Library and Information Science both from University College London. Paola leads on all aspects of ADI's work. Together with the Board, Paola ensures our strategy is implemented and resourced. Paola is ADI's main spokesperson and represents the organisation internationally.



Dementia prevention – where is the science and what are the implications?

Anja Leist

Many in the field are confident that a large number of people could take preventive action against dementia and live in good cognitive health up to advanced older ages. The Lancet Commission on dementia suggests that up to 40% of dementia cases could be prevented if 13 modifiable risk factors such as low education, hearing loss or depression were eliminated¹. Eliminating these cardiovascular, metabolic, social and other risk factors further comes with associated benefits for a wide range of other health outcomes.

According to these estimations, we need to add a prevention lens across the life course: support children to receive high-quality education until well into late adolescence. We need to address the commercial determinants of health: make healthy foods available to everyone, reduce heavy alcohol consumption by norm shifting even if this means lower tax revenues, reduce smoking, reduce availability/affordability of high-calorie low-nutrition foods and sugar- and artificial-sweetener sweetened beverages. We also need to make sure cardiovascular risk factors are monitored and managed, ideally without systemic healthcare barriers such as co-payment. Finally, contextual risk factors linked to climate and global change such as air pollution and exposure to extreme heat need to be minimized to protect population brain health. This list of actions suggests that dementia prevention at large is a transversal topic and should be addressed cross-ministerially.

Preventing dementia also means valorising cognition as an important human capital for the functioning of today's societies, and adjust work, noise and environmental regulations to limiting adverse influences on cognitive performance, and ideally providing optimal environments for individuals to cognitively flourish.

Research desiderata

However, prevention evidence, particularly secondary prevention evidence should still be further stabilised and the next years will bring knowledge on the potential of secondary-prevention lifestyle interventions to reduce

prevalence of dementia. Robust scientific evidence on the modifiability of dementia risk in the presence of risk factors from diverse samples and different geographical regions is important – it would be unethical to suggest time- and resource-intensive interventions to individuals that may not be able to benefit.

More knowledge on the modifiability of dementia risk by improving lifestyle is currently being gathered in research, with many of the pragmatic and randomized controlled trials adapting the framework of the FINGER trial and being part of the Worldwide Fingers Network⁴.

Research needs to respect equity principles, not only because of recognizing the importance of that value but also simply due to cost effectiveness considerations; individuals from socioeconomically less advantaged backgrounds, with lower education have more potential for improvement. These groups are more difficult to recruit, but the highest benefits will come from understanding exactly how to lower their risk and to implement this knowledge. Further, in LMICs where dementia prevalence is higher than in European and Northern American countries – our recent estimate was, after correction of study heterogeneity, 8.96% for all-cause dementia in Latin America and the Caribbean in individuals aged 65 and older⁵ – socioeconomic and lifestyle profiles need to be understood better, and research (infrastructure) in these world regions needs to be supported to design effective dementia prevention strategies.

Secondary prevention in the future will continue to combine lifestyle interventions and medical treatment of risk factors such as anti-hypertensives. A lifestyle trial originating from FINGER tests combining lifestyle interventions with diabetes medication. Prevention research needs to also test if the new, highly effective drugs against diabetes and obesity have the potential to modify dementia risk in the long run.

Unequal opportunities for dementia prevention

Low-barrier awareness programmes are needed to increase brain health awareness as many individuals fear dementia but at the same time know little about potential to improve brain health through modification of lifestyle. In the past these public health messages often were poorly designed, as they made the aware more aware but didn't reach those at highest risk. The public health message "live more healthily" is not only not feasible to realise for some but may even sound sarcastic to those with strong economic and time restraints. Indeed, assigning responsibility to the individual

in dementia prevention efforts neglects the conditions in which people are born, grow, live, work and age, commonly referred to as the social determinants of health. These are rarely changeable by individuals themselves. In contrast, social determinants of health determine to a large extent the quality and quantity of schooling, exposure to strenuous and hazardous work or living conditions, the possibility to exercise and eat healthily. We recently showed with UK Biobank data that individuals living in socioeconomically deprived neighbourhoods have increased risk to develop dementia, even after controlling for lifestyle and many individual-level determinants such as depression³. We need to factor in that individuals can only to a small extent influence their work and living conditions, and vulnerable, socioeconomically disadvantaged individuals need more support than socioeconomically advantaged individuals. Primary dementia prevention must mean, from a policymaking perspective, working on the social determinants of health. Otherwise prevention interventions may maintain or further exacerbate health inequalities.

Women spend more time in care work for minors or older and disabled individuals than men. Evidence from research on unpaid care suggests that women may first invest their time in caring for others before they care for themselves. Gender-sensitive approaches to activating men and women to take responsibility for their (brain) health, while stabilising care systems to alleviate (mostly female) caregiver burden will contribute to successful dementia prevention strategies.

The need to decide on allocation of scarce resources may put decisionmakers in difficult positions moving forward. For instance may we take away funding on developing treatment and rather invest in prevention research? Which generations will likely benefit from investments into prevention or treatment – preventing dementia will benefit those in middle and early old adulthood, whereas treatment and care will mostly be benefitting those in later adulthood and advanced older ages. These decisions will partly be political decisions on prioritizing research and healthcare funds, partly coming from the private sector deciding to invest in the development of dementia treatment or prevention, but ideally will be negotiated with public and patient representatives.

Prevention in the era of medical treatments

Prevention still has an important place in this new era of medical treatments. The strategies will need to be combined: As much prevention as possible, and medical treatment for those who will experience cognitive decline nonetheless.

Prevention may benefit all those who are currently and in the future not eligible or able to receive the new medical treatments. We don't have solid numbers on the rate of individuals benefitting from prevention efforts in terms of dementia risk reduction, and some individuals may have increased vulnerability for cognitive decline or reduced capability to fully engage in prevention. Thus there will very likely always be the need for medical treatment even with the most stringent prevention efforts.

Overcoming barriers to public health dementia prevention efforts

We don't have enough knowledge on possible patient stratification for secondary prevention interventions. Geoffrey Rose's prevention paradox that many need to participate in preventive action for only few to benefit needs to be mitigated by testing more stringent dementia risk prediction scores for enrolment into interventions. Cost effectiveness arguments need to be even more convincing in the field of dementia prevention because of the disconnect between budget spending today and expected benefits only quite far in the future. This is why we also need to know which components of the lifestyle interventions are most effective and could be state (co-)financed.

Prevention efforts will most likely only be bringing returns on investment across one or perhaps even several decades – the political election cycles work against that long-term vision and we encourage decisionmakers to consider their desired legacy to implement prevention measures beyond their own political mandates.

Applying an equity lens in research helps us understand that disease risk, and equally dementia risk, is stratified and individual characteristics may directly or indirectly be associated to dementia risk. Research and policy efforts should systematically consider the PROGRESS indicators place of residence, race/ethnicity/culture/language, occupation, gender/sex, religion, education, socioeconomic status, and social capital to advance the field⁶. The value of health equity will support decision making as it reminds us of who needs efforts the most, even if those groups often have less bargaining power in the public and policy discourse. Less advantaged and minority populations are often more difficult to address and less likely to trust in public health messages. However, evidence on the social determinants of health suggests that the highest benefits will come from understanding how to lower dementia risk of those who are most disadvantaged.

Steps forward

Even if we are still in the process of gathering knowledge on what dementia preventive efforts work for whom, we can be confident that improving lifestyle and cognitive reserve increases resilience to stressors and pathology and has benefits for a range of associated health outcomes. Thus preventive services to support lifestyle changes should be offered to individuals at increased risk, ideally be carried out systematically and country-wide, by activating GPs and neurologists to identify individuals suspected at risk. This is done in Luxembourg with the national dementia prevention programme (www.pdp.lu) that enrolls individuals with confirmed Mild Cognitive Impairment or subjective cognitive decline and which includes regular, comprehensive neuropsychological and lifestyle assessments and a voucher system to improve lifestyle behaviours and increase social, cognitive and physical activity.

According to the OECD, governments still spend less than 3% on health spending for prevention². As prevention researchers, we encourage governments and healthcare decisionmakers to add the preventative perspective to the mostly disease-driven treatment and care perspective. In a context of scarce resources, this additional mission of the healthcare system to prevent disease may be challenging but we should strive to reduce the undoubtedly high burden of a diagnosis of dementia for as many individuals and their families as possible.

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After her PhD studies in Psychology at the University of Trier, she had postdoctoral research stays at the universities of Luxembourg, Zurich, and Rotterdam. Her research focuses on cognitive ageing and dementia from a social and behavioural (risk reduction) perspective. Anja's research interests also involve social and life-course determinants of health, healthcare use, and use of technology at older ages. Anja is PI of several competitively funded research projects, among them a grant from the European Research Council on cognitive ageing and dementia with a focus on lifestyle behaviours and contextual inequalities related to education and gender. She is co-leading an interdisciplinary flagship project at her institution that investigates links between the social environment, microbiome, and dementia. Anja has received an 'innovative publication' award, is elected Fellow of the Gerontological Society of America, and cofounder of the World Young Leaders in Dementia a.s.b.l. (WYLD) network, now a registered non-profit organization facilitating careers of young professionals in dementia. She is member of several steering groups and scientific advisory boards. Anja is a Rotarian, married, and has two children.



A new perspective for targeting “Inflammation” in AD

Christopher J. Barnum and Malú Gámez Tansey

Less than a decade ago, proposing that the immune system was a key target for neurodegeneration was almost completely dismissed – grants were difficult to get funded and capital for clinical development was virtually non-existent. It wasn't until the GWAS reported that more than 60% of the genetic variants associated with Alzheimer's dementia are expressed primarily in immune cells that “inflammation” received the appropriate attention. If the number of clinical trials is any indication, inflammation now rivals amyloid as a target in AD. A review of the targets being investigated reveals a diverse approach that generally falls into one of two strategic categories: i) reduce inflammation or ii) activate immune cells to clear amyloid and tau. That these two categories exist as separate therapeutic strategies suggests a failure to understand the biological state of the immune system in AD.

The immune system: what and how should we target it?

Although biologically complex, it is conceptually simple: The immune system is dysfunctional. Its response is maladaptive and detrimental to the organism. It manifests in two ways, destruction, and neglect. What we call “inflammation” or “chronic inflammation” is the destructive aspect of immune dysfunction. “Destructive” immune dysfunction is epitomized by immune cells unleashing the same lethal attack that eliminates infection on native tissues, resulting in damage and cell death. What's less appreciated about immune dysfunction is that this comes at the cost of its homeostatic responsibilities (neglect) – which is to provide support to every system within the body. Some systems rely on the immune system more than others. In the CNS, local innate cells (eg., microglia and astroglia) have evolved alongside neuronal tissue and are an integral part of brain function. In many ways, immune cells serve a parental role to neurons, whose capabilities are infant-like. Among other things, glia provide trophic support, build and maintain neuronal connections and networks, buffer toxic elements, and clear cellular debris, etc. These homeostatic functions are critical

to brain function and become increasingly neglected in a dysfunctional immune system. Thus, the goal is to restore normal immune function.

Developing therapies that stop inflammation only deals with half of the problem. This is further complicated by the fact that “anti-inflammatory” therapies almost certainly suppress glial and therefore further impair their homeostatic functions which could exacerbate disease or mask the benefits of driving down destructive inflammation. This is not theoretical and best exemplified in Multiple Sclerosis patients whose disease worsened when treated with the non-selective TNF inhibitor Lenercept. On the other hand, therapies that activate the immune system to clear debris for example must consider whether they are simply activating a dysfunction immune cell and the consequences of doing so. Effective inflammatory treatments will need to address immune dysfunction in a way that does not suppress normal glial function – i.e., anti-inflammatory but not Gliasuppressive. This can only be accomplished when we understand the role of an immune target as it relates to both immune dysfunction and homeostasis.

The implication of Immune Dysfunction as a cause, not a consequence of AD

The prevailing view of AD is that microglia start out as protective actors and as the neurons build up aggregated proteins and toxic debris, they become hyper-activated and secrete inflammatory molecules that bombard neurons with cell death signals. Data shows that dysfunction of the innate immune system occurs as we age beginning in our 3rd/4th decade of life (around the time Braak predicts disease onset) and continues to decline as we age. Postmortem studies report that the difference between AD and Non-AD patients is not the amount of amyloid in their brain, it's the presence of inflammation, AD patients have inflammation. If innate immune dysfunction is the root cause of chronic inflammation arising from genetic, lifestyle, diet, environment, stress, and other factors, then it is imperative that our field of neurodegeneration focus on targeting innate immune dysfunction to slow, delay, or prevent age-related neurodegenerative disease. We should consider innate immune dysfunction arising from inflammaging and immunosenescence where there is loss of immunocompetence as a process that is required for crossing the threshold into a neurodegenerative downward spiral. This would then open up a world of possibilities for immune-targeted therapies for individuals at risk for age-related neurodegeneration due to mid-life chronic systemic

inflammatory conditions, including repurposing of drugs in the autoimmune and cancer space.

We are at a threshold where inflammation has taken center stage. The goal should not be to develop drugs to reduce inflammation or activate glial; rather, the goal should be to restore dysfunctional immune cells to their homeostatic, reparative, and protective state. How we target the immune system will determine our success. The strategies of the past will not get us there.

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Dr. Barnum is a neuro-immunologist with broad expertise across neurodegenerative and psychiatric diseases holding multiple positions in academia and industry, including Emory University, FPRT Bio., SonosBio, and Takeda Pharmaceuticals. His focus has been on translating inflammatory therapies into clinical treatments for neurologic diseases using a biomarker-directed approach. Dr. Barnum is currently leading the development of XPro1595, a product he's been working with for more than a decade, first at Emory University with Dr. Malú Tansey and subsequently as a consultant for FPRT Bio., Inc. and INmune Bio, before joining INmune Bio full time in 2018. Dr. Barnum's research has been supported by NIH, The Michael J Fox Foundation, and the Alzheimer's Association.



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Dr. Tansey obtained her B.S/M.S in Biological Sciences from Stanford University and her Ph.D. in Cell Regulation from UT Southwestern followed by post-doctoral work in neuroscience at Washington University. As head of Chemical Genetics at Xencor, she co-invented novel soluble TNF inhibitors that have now advanced to clinical trials in Alzheimer's disease. Dr. Tansey is a fierce advocate for women and other under-represented groups in STEM and has earned several mentoring awards from students and faculty for her efforts in this area.

Some other issues in our quest to share data

Arthur W. Toga & Sidney Taiko Sheehan

Introduction

Data sharing holds the promise to accelerate progress and innovation in scientific discovery. Many scientific communities have embraced the idea that open science and freely sharing raw and processed data can further our quest to derive information and knowledge. Furthermore, governmental funding agencies and private foundations generally embrace the concept of open science and increasingly mandate data sharing as a requirement when research awards are granted.

However, the mere requirement that data be shared is insufficient. As science has evolved into a data-driven economy, it has become clear that there are significant challenges to data sharing beyond those related to technology and infrastructure. Though existing guidelines, such as those enumerated by the FAIR (Findable, Accessible, Interoperable, and Reusable) principles, provide a beneficial set of goals for good data management and stewardship, without certain sociological and practical considerations, mere guidelines may fail to realize the full potential of data sharing.

This paper is in no way intended to be prescriptive, although inevitably personal biases may be evident. Rather, this is an attempt to raise some issues and concerns heard and witnessed from colleagues with whom we have worked as part of our informatics center and programs over the years.

Sociology

The investigator that collects data based upon carefully designed protocols, balanced and appropriate subject recruitment, consistent methodology, and comprehensive documentation to answer hypotheses described in (often multiple applications before success) a funded grant and who may or may not yet have analyzed and written the paper describing the findings, rightfully has some concerns regarding the when, what, and how that data is shared. Many investigators do not want to merely hand over the data they spent considerable resources and time collecting. It is understandable that investigators may have a sense of

ownership and desire for (some) proprietary control. One can disagree with this line of thinking, but it is understandable.

The investigator may be more enthusiastic about sharing data if authorship on the paper that results from the sharing is promised. The investigator may be more eager to share after their own papers have been published. Investigators, laboratory members, centers, institutes, universities, and others often want to be acknowledged. And there are many models to achieve this. Data Use Agreements often stipulate the type of acknowledgement, including authorship or listing as a collaborator in the author list, for example. Investigators might be wary of sharing if disparities in resources are apparent. What if recipients of the data have overwhelming capacity for rapid and sophisticated analysis compared with the data provider? The investigator may be more motivated if the data shared results in confirmation of their findings as opposed to contradicting them. This may not be good scientific practice, but one would not be surprised if it occurs. The investigator might be more willing to share if the benefits in future grant getting, reputation, appreciation, and even academic recognition were provided. Over the years, countless discussions, workshops, and 'white papers' on modifying academic review in University promotion processes to include data sharing have occurred, with little consequence.

The funder, on the other hand, may have other concerns, such as maximizing the value, significance, and contribution of the science (and data) produced by the funded project. Re-use of data is a more efficient use of time and resources and can reduce research cost. Funders may want to ensure the funding source is well and clearly represented in all publications, including those from re-use of the data. They may want to make certain that re-distribution of data is limited or prohibited, so as to manage data integrity and adherence to data use stipulations.

As data sharing requires an ever-increasing abundance of time and resources, additional incentives may be required to prioritize data sharing. What reward systems can be put into place? How can data sharing requirements be improved so it is clear everyone benefits? Science is conducted mostly within a competitive system to receive funding. Should there be some method in place for data providers to avoid losing the advantage of high scientific value data?

What are the real objectives of data sharing? The response to this foundational question differs between funders,

data providers, users, regulators, and patients. There are differences across scientific disciplines, cultures, and countries. There are differences between commercial concerns and academics. Each constituent has a different perspective, and we must acknowledge this and account for their motivations and concerns.

What Data?

Data sharing must be intentional. Data sharing that was intended prior to the research being initiated is often easier and better than after the fact. Is the data uniform, consistent, well organized, comprehensively described, modern, useful, and valuable? How much effort is it worth to make the data shareable? The mere presence of accessible data does not speak to its worthiness. All data is not of equal value, nor do we have systems in place to evaluate the potential benefits of data sets. Do we know how to do that? Should we do that? How do we account for data providers who put significant effort into data harmonization, and utilization compared to data providers who put forth the minimum? Scientific communication is built upon a culture of peer review; might we apply this same process to data?

We must also consider what should be provided in the data sharing process. Quality control metrics, complete provenance, and metadata can all serve to enhance both the primary utilization of the data as well as subsequent and unanticipated re-use. The adoption of standards, when appropriate, and use of carefully curated ontologies, detailed dictionaries, and accepted common data elements are essential to achieve the widest possible data sharing. But how can we encourage this?

When acknowledging that not all data is created equal, we should also consider if we must apply democratic methods to data sharing. For example, if data is obtained from studies and/or instruments of significant cost, is that data treated the same as data obtained from inexpensive experiments? Should the same effort and cost be applied to both?

Compliance, Regulation, and Legal Considerations

Compliance, privacy, and legal considerations are constantly evolving. While some of these considerations might encourage more data sharing, often they inhibit it. Requirements are driven by policy and in many instances, motivated by needs to limit liability, both legal and financial, as well as maintaining positive public perception and reputation. Participants in studies also have changing expectations for how, where, and when their data can be

used. All these considerations differ by institution, country, and time. How can we comply with rules that change? Once data has been shared and the rules become more restrictive, how can we call back data that no longer complies?

Investigators can adhere to their respective legal, privacy, and regulatory requirements while sharing some form of data. Others might interpret those requirements more stringently and adopt highly protective policies that inhibit data sharing. Guidance, clarity, and consistency in such matters is frequently unavailable.

Mostly, the compliance, regulatory, and legal aspects of data sharing are focused on the protection of the data and the participants, if human. There are few such considerations for the investigator. How can we ensure that the Data Use Agreement is adhered to? That those who have been entrusted with proper use of the shared data, use it as stipulated in the agreement, including, but not limited to, providing credit to the data provider? Do we need regulations to absolve data producers from misuse of data in situations such as erroneous data resulting in harmful clinical recommendations?

Ethical Concerns

While guidelines like FAIR provide support for researchers aiming to increase accessibility and reusability, we might begin again with a more fundamental question: when *should* data be shared? And when should it not? Are data sharing mandates truly beneficial when the potential for data reusability is low? Does this not put undue pressure on the resources of investigators, the sharing systems, and even the funders?

Should data be shared before it is complete, without any QC that might identify errors? The 'when' of data sharing might relate to how acute the investigation is relative to clinical need. Rapid data sharing in COVID-19 research was important to facilitate prompt assessment of safety and efficacy of vaccines, yet swift data sharing prior to completion may not apply to many situations and could even be detrimental.

There is often significant ambiguity surrounding issues of financial burden, privacy concerns, and the potential for data to be misused and/or misinterpreted. A systematic approach to addressing these concerns could encourage more data sharing, while keeping researchers accountable for their work. Further, data providers may take issue with the intended secondary use of their data.

Ethical disagreements could arise between groups regarding the proportional risks and benefits of the secondary use of data. How are these situations to be mediated?

Infrastructure

The need to develop informatics infrastructure to support data sharing is often a primary topic in policy discussion. What types of databases systems, schemas, and security measures are best suited? What types of management systems can be created? Is the specific scientific community really served, and can we tailor each implementation to the needs of that discipline? Should data infrastructures be centralized, linked, federated? No single solution can possibly fit all needs. Do we have the resources to develop specialized systems? And how could they be interoperable?

The Cloud is often touted as the solution to storing and computing on shared data, but have the costs been truly assessed? Depending on the type of data, how often it changes, whether data for a project is still being collected, whether users want or expect to be able to download the data, how large and how many files exist and of what type, and how computationally expensive are the analyses has a lot to say about costs. Currently, it is unclear who pays and when and what is financially equitable.

While cloud-based storage provides benefits such as relative ease of access, possible costefficiency, scalability, etc., implementation must address issues of security, identity management, access control, and contractual and legal issues. Cloud-based solutions are for-profit companies. Is that a problem, and if not now, can it become one? Do these companies have the domain expertise? And how might their motivations differ from data providers and/or data users? For this reason, many investigators feel the need to retain possession of the data and handle sharing personally, or work with an outside trusted investigator for assistance. Often the implementation of the sharing infrastructure; storage, search, access control, distribution, logging, support, and other aspects can only be achieved by informatics experts in the same or similar scientific discipline.

Expertise in informatics, machine learning, and software development, are often required to develop efficient and adopted data sharing infrastructure. It should be noted that building an infrastructure, regardless of where it is located, is only the beginning. Systems invariably require constant updating, modification, and adaptation to new requirements. Many researchers are not specifically trained

in these areas, creating a knowledge gap. This could impact not only the proper collection of data, but also data sharing, and appropriate use of data shared. How do we account for disparities in training?

With large data sets, co-localizing compute capabilities with the data avoids the transmission across limited networks. Does that demand only cloud-based solutions? There are countless data centers at universities that are not fully utilized, can these contribute?

The challenge is not just storing the data; it is also finding it. Search is complicated and often specific to the study and discipline. Within a data storage system, data are only usable if a researcher can search and retrieve them, can make sense of them, and can analyze them within a single study or combine them across multiple studies. Thus, data must be in a computable form amenable to automated methods of search, analysis, and visualization. Interoperability of shared data should enable data aggregation from multiple studies and meta-analyses across them. Search needs to work across multiple studies.

Conclusion

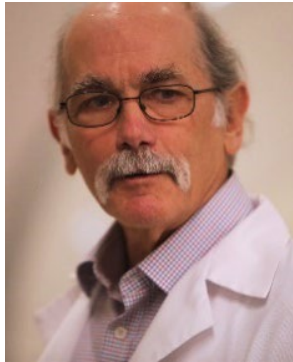
The concept of data sharing is positive at most every level. The dissemination and communication of the knowledge gained from scientific studies are vital. Open access data can bring together researchers from many complementary and adjacent disciplines, who might not otherwise have the opportunity to collaborate and further each other's work.

But how will we know we are taking the best approach? Are there metrics we can establish that will inform us that we are doing something additive, and not just checking the data sharing box? We might measure how often data users vote with their feet. How many downloads, metaanalytic papers, data re-use findings, clicks, and active accounts are there from a particular system? Publishing such statistics might help us realize when we are on the right track.

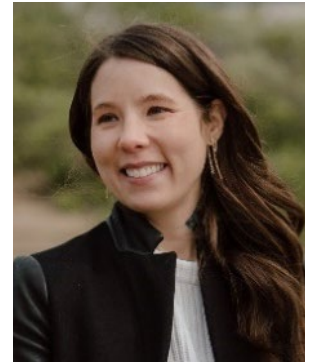
Certainly, researchers across the scientific spectrum can come together to help find innovative, effective, and most importantly, welcomed, solutions to the concerns we highlighted. Data sharing mandates alone do not facilitate discovery, and without addressing the challenges noted above, it will be difficult to fully realize the true power of shared data.

**Arthur Toga Provost, Professor of Ophthalmology, Neurology, Psychiatry and the Behavioral Sciences
University of Southern California (USC)**

Dr. Toga's research focus is on neurodegenerative disease and specifically works on Alzheimer's disease. He has pioneered some of the most widely used informatics systems in the world (e.g., IDA and GAAIN), supporting more than 150 multisite trials in AD and other neurological diseases and psychiatric disorders. His interdisciplinary work led to the creation of the Laboratory of Neuro Imaging (LONI), which he also directs and is one of the most advanced multidisciplinary neurological research centers. Funded by the National Institutes of Health (NIH), the Alzheimer's Association, the Michael J Fox Foundation among others, as well as industry partners, LONI houses one of the largest computing facilities and largest brain image repository in the world. He is an author or co-author of more than 950 peer-reviewed papers, 1100 abstracts and 80 book chapters or books, among them Brain Mapping: The Methods. He is the founding editor of the journal NeuroImage. Dr. Toga has received numerous awards for his research and teaching, including the Pioneer in Medicine Award, Smithsonian Award for Scientific Innovation and Giovanni DiChiro Award for Outstanding Scientific Research. He holds the Ghada Irani chair in Neuroscience and has been one of the world's top researchers on the AD Scientific Index, Top 200 Best Scientists in Neuroscience on Research.com, and listed as one of Thomson Reuters' and Clarivate Highly Cited Researchers for many years.



**Sidney Taiko Sheehan, Communications Manager
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The New Era in Alzheimer’s Disease Therapeutics: Planning and Implementing Systems Accommodations to Facilitate Patient Access

Jeffrey Cummings & Husseini Manji

Introduction

Alzheimer’s disease (AD) is a major global public health threat currently affecting 50 million individuals worldwide, a number that is projected to grow to 150 million individuals by 2050 if unchecked [1]. Great scientific effort has been invested in developing ways to delay the onset of AD, slow its progression, or improve its symptoms. These endeavors are beginning to deliver new treatments, and we have entered a new era of AD therapeutics ushered in by the discovery and development of anti-amyloid monoclonal antibodies (MABs)[2]. Immunotherapy slows the progression of early AD (mild cognitive impairment and mild dementia due to AD), reducing measures of cognitive impairment by 25 to 40%. To date, aducanumab (Aduhelm) and lecanemab (Leqembi) have received accelerated approval in the United States (US) and lecanemab and donanemab are under review for standard approval [3-5]. All three agents are being evaluated in other countries and are expected to be approved for use with restrictions.

Anti-amyloid MABs are unprecedented disease-modifying therapies (DMTs) that pose new requirements for diagnosis, monitoring, and management. Advanced technology and expertise are needed to administer MABs safely and with maximum opportunity for efficacy [6] and, thus, make new demands on health care systems. We describe the use of these agents, the resources needed for their use, the anticipated scientific advances that may affect the use of MABs, and the promise of other types of treatments for AD.

Appropriate Patients

Table 1 shows the principal features of patients for whom treatment with MABs is most appropriate and

the corresponding resources required [7, 8]. Patients must have early AD confirmed by an amyloid biomarker (amyloid positron emission tomography [PET] or cerebrospinal fluid [CSF] measures). In addition, magnetic resonance imaging (MRI) is required prior to initiating treatment to exclude extensive cerebrovascular disease that may increase the risk of side effects of anti-amyloid MAB treatment. Previous seizures or past or current inflammatory disorders exclude the patient as a treatment candidate because these may predispose the patient to the serious side effects that infrequently occur with therapy. Finally, patients cannot receive anticoagulants while receiving anti-amyloid MABs.

Table 1. Principal features of patients for whom treatment with MABs is most appropriate and the corresponding resources required for diagnosis.

Patient Characteristic	Health Care Resources Required
Early AD	Clinical diagnostic expertise
No medical history of inflammatory diseases or seizures	Clinical expertise in patient assessment
No extensive brain vascular disease (microhemorrhages or white matter abnormalities)	MRI and expertise in MRI interpretation
Diagnosis confirmed by amyloid biomarker	Amyloid PET or CSF amyloid measures with expertise in PET interpretation and CSF analysis
Not receiving an anticoagulant (blood thinner)	Clinical expertise in patient assessment and review of requirement for anticoagulant treatment
Has APOE genotyping to determine risk of ARIAs	Availability of genotyping and genetic counseling

AD – Alzheimer’s disease; APOE – apolipoprotein E; ARIA – amyloid related imaging abnormalities; CSF – cerebrospinal fluid; MRI – magnetic resonance imaging; PET – positron emission tomography

Patients who have an apolipoprotein E4 (APOE4) genotype are at higher risk for amyloid related imaging abnormalities (ARIA), a side effect of anti-amyloid MAB therapy (discussed below). APOE4 homozygotes carrying two copies of the gene are at particularly high risk for ARIA. Thus, treatment candidates should be genotyped prior to the decision to initiate therapy so that an informed risk discussion can occur with the patient and care partner.

Administration, Monitoring, and Management of Anti-Amyloid MABs

Anti-amyloid MABs are administered monthly by intravenous infusion (aducanumab, donanemab) or twice monthly (lecanemab). Aducanumab and donanemab are titrated to reach the defined optimal dose; lecanemab does not require titration. Infusion reactions may occur and can be treated or prevented with acetaminophen or, if required, corticosteroids.

The principal side effect of anti-amyloid MABs is the occurrence of ARIA of the effusion type (ARIA-E) or hemorrhagic type (ARIA-H). ARIA is thought to represent the escape of fluid or blood into the brain through blood vessel walls made more permeable by removal of vascular amyloid by the MAB. As noted above, APOE ϵ 4 gene carriers are at highest risk for this complication. Most ARIA events have no associated symptoms, but MRI must be performed periodically during the initial months of therapy to detect their occurrence, as continued dosing in patients with ARIA may exacerbate their severity. If symptoms occur with ARIA, or if the ARIA observed on MRI are moderate to severe, treatment is interrupted until ARIA-E resolves or ARIA-H stabilizes. Treatment can then be resumed. The MRI monitoring schedule differs for each of the anti-amyloid MABs.

In rare cases, ARIA may be serious, and fatalities have occurred. For this reason, health care systems and clinicians providing anti-amyloid MAB treatment must have resources to manage severe ARIA. Intensive care capacity, access to emergency MRI, and expertise in managing brain edema and seizures or status epilepticus are required [7, 8].

Patients who are candidates for treatment with anti-amyloid MABs and their care partners must be educated about the therapy, including the diagnostic process, genotyping, monthly or every-other-week infusions, periodic MRIs during treatment initiation, and the occurrence of ARIA and infusion reactions. Channels for rapid communication between the patient and the treating clinician are required to exchange information about symptoms possibly indicative of ARIA.

Another key consideration is when to stop treatment. Severe, symptomatic ARIA, any macrohemorrhage, more than two ARIA episodes, more than one area of bleeding near the brain surface (superficial siderosis), or accrual of more than 10 new microhemorrhages since treatment initiation are indications to stop treatment. In addition, if the patient develops a condition that requires anticoagulant therapy, treatment

should be terminated; if the anticoagulant treatment is temporary, treatment can be resumed once the anticoagulant is stopped.

It should also be noted that the efficacy and safety of treatment with anti-amyloid MABs are known only for patients with early AD. When the patient progresses to moderate or severe AD, providers should discuss stopping treatment with the patient and care partner. In the case of donanemab, patients are treated until an amyloid PET demonstrates the absence of detectable levels of plaque amyloid (usually after six to nine months of treatment). Treatment is then stopped until there is biomarker evidence of plaque re-accumulation [3].

Future Research May Simplify the Use of Anti-Amyloid MABs and Create Treatment Alternatives

Rapid progress in AD research and discovery promises to develop new technologies to simplify the use of anti-amyloid MABs and to advance new types of therapies. As a key example, subcutaneous formulations of anti-amyloid MABs are under study and may become available. Subcutaneous administration would be easier for many patients, would not require infusion resources, and would allow more patients to be reached and treated. In addition, combining anti-amyloid MABs with technologies that allow a larger amount of the administered drug to cross the blood-brain barrier decrease production demands and expense, which may reduce the cost of treatment. Currently, approaches to improving blood-brain barrier penetration of MABs are being advanced. Blood tests may replace amyloid PET or CSF amyloid studies to confirm the diagnosis of AD, making it easier and less expensive to identify patients who are treatment candidates. Similarly, blood tests may reveal when amyloid has been successfully removed from the brain and if it is beginning to reaccumulate, thus suggesting that treatment should be re-initiated if it has been interrupted. Finally, improved anti-amyloid MABs may lead to agents that are more efficacious, require less frequent administration, or have less ARIA liability.

It should also be noted that while plaque amyloid has now been validated as a treatment target for AD, many other treatment targets remain to be explored, including the tau protein, brain inflammation, brain metabolism, synaptic function, and others. These therapies could supplant anti-amyloid MABs if shown to be sufficiently efficacious or might be used in simultaneous or sequential combinations with anti-amyloid MABs to have greater impact on preserving patient cognition and function.

Learning Social and Healthcare Systems

The advent of DMTs impacts the entire ecosystem of memory care and treatment of AD. Patients with memory complaints or abnormalities are assessed to determine which have AD and which have other causes of memory loss. Definitive diagnosis requires biomarkers. Treatment of early AD patients with MABs necessitates MRI, infusion resources, expert management, and availability of intensive care for rare patients with serious side effects. Public education, clinician educational initiatives, and information for many other members of the health care ecosystem – pharmacists, radiologists, nuclear medicine specialists, nurses, clinicians – are required to ensure good clinical practice. Current approaches are likely to evolve as new biomarkers become available and new treatments are developed and approved. The new era of MABs for the treatment of AD is an advance that will improve the lives of those affected by this common disorder of older individuals; it is progress that requires corresponding adjustments in policy and planning.

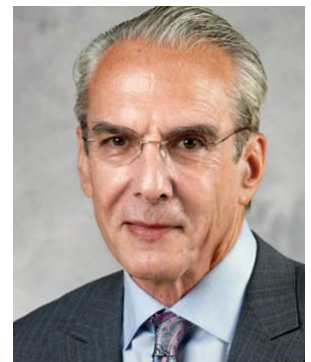
Advances in understanding human biology and disease is likely to lead to many new medical therapies for cancer, cardiovascular disease, stroke, and neurodegenerative disorders, including AD. These treatments aim to reduce disease burden, improve function, enhance wellbeing, and increase longevity. These are goals to be embraced for all humanity. This anticipated progress requires responsive social and healthcare systems that can absorb new therapies, flexibly respond to the emergence of novel therapeutic approaches, and establish planning mechanisms that include scientists, regulatory authorities, and payors to build learning enterprises that can provide the best care that science can create.

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Dr Cummings is a world-renowned Alzheimer's researcher and leader of clinical trials. He has been recognized for his research and leadership contributions in the field of Alzheimer's disease through the Henderson Award of the American Geriatrics Society (2006), the Ronald and Nancy Reagan Research Award of the national Alzheimer's Association (2008), and the Lifetime Achievement Award of the Society for Behavioral and Cognitive Neurology (2017). In 2010, he was honored by the American Association of Geriatric Psychiatry with their Distinguished Scientist Award. In 2018, he was honored with the Leadership and Achievement Award by the International Society of CNS Drug Development, and he received the Bengt Winblad Lifetime Achievement Award from the national Alzheimer's Association. In 2019, the International Psychogeriatric Association awarded him with the Distinguished Service Award and he received the Alzheimer's Drug Discovery Foundation's Melvin R. Goodes Prize that honors an innovative researcher who has made a significant and lasting impact in the field. He was featured in the *Gentleman's Quarterly* (June 2009) as a "Rock Star of Science™."



Husseini K. Manji, M.D., F.R.C.P.C. Co-chair, UK Govt Mental Health Mission, and Professor, Oxford University and Visiting Professor, Duke University

Husseini K. Manji, MD, FRCPC is Co-chair of the UK Govt Mental Health Mission, Professor, Oxford University and Visiting Professor, Duke University. He is past Global Therapeutic Head for Neuroscience at Janssen Research & Development pharmaceutical companies, and Global Head, Science for Minds, J&J. Before joining



J&J, Dr. Manji was Chief of the Laboratory of Molecular Pathophysiology at the National Institutes of Health (NIH) and Director of the NIH Mood and Anxiety Disorders Program, the largest program of its kind in the world. He has been inducted into the National Academy of Medicine (NAM, formerly IOM), is a member of the National Institutes of Health Novel and Exceptional Technology and Research Advisory Committee, the World Dementia Council, the World Economic Forum (WEF) Global Future Councils, the Board of Mass General-Brigham Incorporated; the Board of Trustees of Harvard University/McLean Hospital, the Board of the Dana Foundation, the Scientific Advisory Board of the Stanley Center at the Broad Institute of MIT and Harvard. He is recent chair of the National Academy of Medicine Neuroscience, Behavior, Brain Function & Disorders group, co-chair of the Healthy Brains Global Initiative, and has held numerous leadership positions within the NIH, NAM, the FNIH Biomarkers Consortium Executive Committee. The major focus of Dr. Manji's research is the investigation of disease and treatment-induced changes in synaptic and neural plasticity in neuropsychiatric disorders. Dr. Manji has helped to discover, develop, and launch several new medications for serious neuropsychiatric and neurodegenerative disorders. These include the first novel antidepressant mechanism in over 30 years, the first medication in Neuroscience granted FDA "Breakthrough designation", a once every 6-month treatment for schizophrenia, novel mechanism(s) for Alzheimer's Disease, multiple sclerosis among others. Dr. Manji also has been actively involved in developing biomarkers to help refine these multifactorial diseases, and to develop a holistic approach towards neuropsychiatric and neurodegenerative disorders. Dr. Manji has received a number of prestigious awards, including the NIMH Director's

Career Award for Significant Scientific Achievement, PhRMA Research & Hope Award for Excellence in Biopharmaceutical Research, the American Federation for Aging Research Award of Distinction, the A. E. Bennett Award for Neuropsychiatric Research, the Ziskind-Somerfeld Award for Neuropsychiatric Research, the NARSAD Mood Disorders Prize, the Mogens Schou Distinguished Research Award, the ACNP's Joel Elkes Award for Distinguished Research, the DBSA Klerman Senior Distinguished Researcher Award, the Briggs Pharmacology Lectureship Award, the Caring Kind Alzheimer's Disease Leadership Award, and the Global Health & the Arts Award of Recognition, and has also been recognized as one of 14 inaugural "Health Heroes" by Oprah magazine. Throughout his career, Dr. Manji also has been committed to medical and neuroscience education and has been a member of the National Board of Medical Examiners (NBME), the Howard Hughes Medical Institute Research Scholars Program, and numerous national curriculum committees. He founded and codirected the NIH Foundation for the Advanced Education in the Sciences Graduate Course in the Neurobiology of Neuropsychiatric Illness and has received several teaching and mentoring awards. He has also served as Editor, and on editorial boards of numerous scientific journals, and has over 350 articles on the neurobiology of severe neuropsychiatric and neurodegenerative disorders and development of novel therapeutics. Additionally, publications on holistic approaches to treatment/care, including digital and psychological approaches (> 50, 000 citations; H-index: 125).

Future with timely diagnosis using blood tests for Alzheimer's disease

Charlotte Teunissen

Introduction

Dementia is an enormous problem in view of the aging population. Dementia can be defined clinically based on cognitive and behavioural dysfunction, and has multiple causes. However, the main cause is Alzheimer's dementia (AD), which is the cause in 60-80% of the dementia cases. AD can be defined and diagnosed biologically, which is similar to other common diseases such as cancer.

Very accurate tools are available for this diagnosis of AD diagnosis, such as analysis of biomarkers. Biomarkers are markers of biology – either normal, pathological or a response to an therapeutic intervention. These AD biomarkers can be measured in the cerebrospinal fluid (CSF) or by brain imaging (PET), detecting abnormal values of the core pathological proteins of AD, namely amyloid beta(42) and phosphorylated tau. However, the lumbar puncture to obtain CSF and the PET scans are expensive, invasive and require to be performed in specialty clinics, which poses a burden not only on the patient but also on the healthcare systems. However, there has been a tremendous development in biomarker detection technologies, through which it now becomes possible to measure these core pathological proteins in blood of AD patients. The results obtained for these markers show remarkable consistency across >200 studies performed over the past few years. For example, studies in independent cohorts and with independent technologies show that plasma pTau is specifically increased in AD patients, for a factor between 3-7 fold. This result was obtained by comparison with the gold standard diagnostic methods, such as either a clinical AD diagnosis that was confirmed by amyloid and tau measurements in CSF or amyloid PET. Several different assays, analysis techniques, have been developed and the sensitivity and specificity of several of the high performing assays is over 90%, which is similar as the accuracies for CSF and PET analysis, and far better than the clinical evaluation. Moreover, these blood plasma pTau elevations have prognostic value in early AD stages for cognitive decline.

The measurement of additional blood based biomarkers helps to get a completer picture for other major dementia types. For example, to diagnose a specific other type of dementia (frontotemporal dementia), blood analysis of yet another protein, neurofilament light chain, has value. Moreover, for prognosis of cognitive decline and brain decay (atrophy) for several dementias, another protein called glial fibrillary acidic proteins adds value.

The advantageous are obvious: blood draw is a low-cost and minimally invasive procedure, which enables sample collection outside specialty clinics, and analysis in individuals with a larger distance to the healthcare systems. Preliminary results showed the high negative predictive value in individuals presenting with cognitive complaints at primary care facilities, and thus early stage negative diagnosis can help reducing the time to diagnosis and burden for the healthcare systems. Almost any country in the world has logistics for blood transport central labs, which makes the analysis feasible and cost-effective. Moreover, many different markers can be measured within one drop of blood, which allows a completer differential diagnosis. For example, the already excellent specific diagnostic accuracy for AD by the analysis of the core proteins pTau and amyloid in plasma can be enriched with information provided by neurofilament light levels, and GFAP will add to gain a completer picture of prognosis. Due to the enabling technologies underlying the successful development of these biomarkers, we can expect that the toolbox offered by blood biomarkers will be further enriched in the near future – e.g. by adding biomarkers for other major dementias, and to further refine the prognostic value.

What is the envisioned context of use?

Use for treatment decisions

These positive developments in blood biomarker testing coincide with the recent first approvals of disease modifying anti-amyloid drugs by the FDA, following positive trial results. These two developments synergistically affect each other. A blood test is envisioned to be useful for screening of individual AD patients for eligibility for these drugs. The targeted patient population are individuals with early clinical stages of AD, and the care setting will be specialty clinics. Published appropriate use recommendations state that confirmation by either CSF or PET analysis is still recommended in the short term. This is due to the novelty of the blood tests, and that gaining prospective evidence in these situations is still needed for validation

and to refine the specifics. This will be crucial to decide for future implementation of these blood tests without other confirmatory tests (CSF or PET). The plasma tests can next inform on expected treatment effects, and for monitoring effects of such treatments on the AD biology.

Technical readiness?

Similarly, analytical technical developments have accelerated. For example, standard operating procedures have been defined and are currently further refined. This was deemed very relevant due to historical issues with analysis of these AD proteins in the CSF. We defined the bandwidth of variability allowed for e.g. time needed for transportation of a blood sample to a central lab (up to one day), or storage temperatures (room temperature vs deep freezing give similar results). Moreover, several types of technologies are available, which vary in ease of single patient sample analysis vs large cohort analysis, costs and throughput time. The choice of assays will depend on the local settings and logistics, but it is the expectation that high precision assays will ultimately be available worldwide. The competition in developing such assays additionally helps limiting the costs for the healthcare systems.

Clinical readiness?

We expect that implementation of these blood tests in the first specialty clinics is feasible in the short term, say one or two years. Current prospective studies will provide learnings to refine this implementation, e.g. how the blood test value is perceived by doctors and how visualisation of the results will help in decision making. Moreover, cost-effectiveness analysis evaluations are performed to understand the economic value in different scenarios, for example in the case that a blood test result is available before the diagnostic work-up, thus integrated with current clinical evaluations, or after this first triage.

There is also a need for education and communication tools, to be able to discuss the use of the markers and the results with patients, but also to support the healthcare professional in interpretation of the tests.

Due to the low-invasiveness and low costs, the blood tests will probably find broader usage, at the level of the primary care. This will depend on local healthcare systems, relating to the role of primary care in triage of patients to specialty clinics, but also to local refunding systems. Several global key stakeholders currently discuss such implementation and provide expert guidance, such as the WHO, World

Dementia Council, and the Alzheimer Association. It is very important that the healthcare systems get prepared for this revolutionary new options to improve the diagnosis, monitoring and care for patient with AD and other dementias.

Charlotte Teunissen, Professor of Clinical Chemistry Amsterdam University Medical Center

Charlotte Teunissen's drive is 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, often by -omics methods, followed by biomarker assay development and analytical validation, and lastly, extensive clinical validation and implementation of novel biomarkers in clinical practice. She has extensive expertise with assay development on state of the art technologies, such as mass spectrometry and antibody-based arrays for biomarker discovery, ultrasensitive immunoassays, and in implementation of vitro diagnostic technologies for clinical routine lab analysis. She is responsible for the large well-characterised biobank of the Amsterdam Dementia cohort, containing >5200 paired CSF and serum samples of individuals visiting the memory clinical of the Alzheimer Center Amsterdam (a.o. controls, patients with Alzheimer, Frontotemporal, Lewy Bodies). To ensure the quality of the biosamples, the group studies pre-analytical effects, which are key to implementation. Charlotte is leading several collaborative international biomarker networks, such as the Society for Neurochemistry and routine CSF analysis and the Alzheimer Association Global Biomarker Standardization and Blood Based Biomarkers consortia. She is the coordinator of the Marie Curie MIRIAD project, aiming to train 15 novel researchers into innovative strategies to develop dementia biomarkers (10 academic centers + 10 non-academic centers), and the JPND bPRIDE project, that aims to develop targeted blood based biomarker panels for early differential diagnoses of specific dementias and is a collaborative project between 7 European and 1 Australian centers.



The path forward in an era of treatments

Stephen Salloway

Alzheimer's disease and related disorders (ADRD) threaten the vitality of the aging population with staggering health care costs for individuals and health systems. There is an urgent need for earlier diagnosis of ADRD and for treatments that delay or prevent the progression of dementia to later stages when care is so costly and burdensome. Fortunately, a steady stream of scientific advances has opened a new era for the diagnosis and treatment of Alzheimer's disease (AD) but many challenges remain to bring these transformative approaches to communities around the world. The World Dementia Council is working globally with scientists, clinicians, policy makers, foundations and regulators to provide interventions that improve care and quality of life for patients and families at risk or those dealing with AD and related dementias. There are many steps that G-7 Health Ministers and other country leaders can do to accelerate this process. This essay will highlight some of the steps necessary for success in the fight against AD.

Having devoted my career to developing new diagnostic tests and treatments for Alzheimer's disease, I am very excited that we now have our first treatments that slow the progression of the disease by substantially lowering amyloid plaques, a key pathological component of Alzheimer's disease. Health care systems and practitioners will need additional resources and training to safely and effectively deliver these treatments and new networks will be required to monitor treatment outcomes. New, cutting-edge treatments, both biomedical and lifestyle, will be required, alone or in combination, to achieve even greater clinical benefits. This will require substantial investment in discovery science, clinical trials and pragmatic studies focusing on implementation of promising findings. New approaches for sharing treatment trial data are required, on par with observational studies, to achieve the greatest impact.

The majority of patients at risk for or experiencing cognitive impairment are seen by primary care clinicians. Increasing the engagement of primary care providers in AD research is essential for improving the standard of care for dementia. Fortunately, there are new blood tests and digital tools that can be used in the primary care setting to help identify patients most likely to benefit from disease-modifying

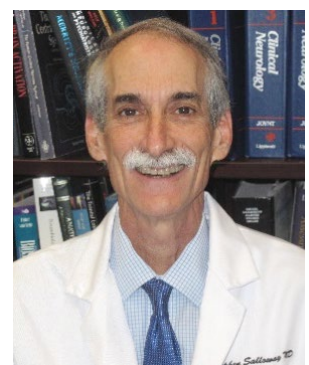
treatments. Further, it is critical to move expeditiously to support the development of new blood tests to reliably monitor treatment response and determine when treatments can be discontinued.

The explosion in artificial intelligence and big data can be harnessed to benefit patients with AD. New partnerships need to be formed with companies capable of analyzing large datasets that monitor important information on day-to-day functions from personal assistants, wearable devices, household appliances and automobiles to guide care and safety.

We are at the dawn of a new treatment era for Alzheimer's disease with an opportunity to move from disease modification to prevention. New approaches are needed to make these treatments accessible to patients around the world with strategies to overcome dramatic inequities in access to care. A concerted public awareness campaign is needed to transform the nihilistic perception of Alzheimer's as an inevitable and untreatable part of aging into a manageable chronic neurological condition requiring early diagnosis and treatment. Policy makers, clinicians, researchers and patient advocates need to form new public-private partnerships that embrace these challenges to find practical and innovative solutions that promote the brain health, vitality and quality of life for aging populations around the world.

Steve Salloway, Martin M. Zucker Professor of Psychiatry and Human Behavior, Professor of Neurology Kent Hospital Rhode Island

Stephen Salloway is Associate Director of the Brown Center for Alzheimer's Disease Research, the founding Director of the Memory and Aging Program (MAP) at the Butler Hospital, a Professor of Neurology and the Martin M Zucker Professor of Psychiatry and Human Behavior at the Warren Alpert Medical School of Brown University, Providence, RI. Professor Salloway's research focuses on biomarker and drug development for prevention and early treatment of Alzheimer's disease, particularly the use of



positron emission tomography (PET) ligands, plasma and CSF biomarkers for amyloid and tau to study the evolution of Alzheimer's pathophysiology in autosomal dominant and sporadic Alzheimer's disease. The MAP also has a lead role in testing targeted treatments, such as monoclonal antibodies, antisense oligonucleotides and novel anti-inflammatory agents. Professor Salloway serves on the steering committees for the National Institutes of Health Alzheimer's Disease Neuroimaging Initiative, the Dominantly Inherited Alzheimer Network, and the Alzheimer's Clinical Trial Consortium. In 2023, he was chosen as the recipient of the Leon Thal Award for Alzheimer's Research from the Cleveland Clinic Lou Ruvo Center for Brain Health, an award named to honor the memory of Dr. Leon Thal, a pioneering neurologist and neuroscientist and influential leader in the field of AD research.

The beginning of a treatment era for Alzheimer's disease

Cath Mummery

Evidence suggesting vaccination could remove amyloid from the brains of mice was published in Nature 24 years ago. Since that time, multiple attempts using similar approaches in humans have failed to show benefit. As a triallist and cognitive neurologist, the past 20 years have been a long and sometimes dispiriting journey. However, those years of negative trials were not wasted – we have learned invaluable information, incrementally improving trial designs and our understanding of the pathophysiology of Alzheimer's disease. Now we are finally starting to see these efforts bear fruit, with three disease modifying therapies (aducanumab, lecanemab, donanemab) having gained FDA accelerated approval, converging results from the anti-amyloid trials strengthening the findings, and full approval on the near horizon for at least one. This is a solid foundation on which we can build.

The results of trials of the latest generation of monoclonal antibodies have shown consistently that lowering amyloid in the brain sufficiently can change the course of the disease, altering downstream markers and slowing cognitive decline. They also tell us what is needed for a trial to be successful: the rate and degree of amyloid lowering matters, and sustained amyloid lowering is needed to accrue cognitive benefit over time. This is a pivotal moment – being able to state we can treat Alzheimer's, to whatever extent, is a seismic change for professionals and patients alike. The message this sends should be a catalyst for cultural and service change in dementia: promoting early and accurate diagnosis, integrated multidisciplinary care and improved resources for our patients and families.

Many questions arise from these results

The importance of this success to the AD community is not to be underestimated; however, it is vital messaging to the public remains measured - the effects of these drugs are modest, and a minority of patients are likely to be eligible, at least initially. Whether the drug effect is meaningful is likely to be debated for some time; as a clinician, my priority is whether it leads to a tangible change my patients would appreciate, usually in terms of function - whether one can

take a phone call, or make a meal, for example. Changes on measures of function and carer burden across trials were encouraging in that regard. Related to that, it is important to consider when to treat: the often-stated wish of individuals with early AD is that they have more time at a stage when they can function with a high quality of life; likewise, when to stop treatment is fundamental – for most, being 'held' at a more advanced stage would not be desirable.

In terms of response, not all are created equal – we need to work out how to identify those who benefit most and those who are more prone to side. We do not yet know whether the effects will be cumulative over time; data from those on drug long-term will be crucial to understanding the trajectory over years.

Finally, how do we give these drugs? Do we, as with donanemab, lower amyloid to a particular point, then stop and monitor for re-accumulation? This would lower patient and hospital burden, and cost. Once depleted of amyloid, do we start an alternative target treatment such as anti-tau or use two drugs in combination? The latter is now being done in the DIAN-TU trial in those at risk of autosomal dominant AD – we hope it increases chances of success; it also increases complexity. How we navigate these questions and continue to broaden our range of treatment options is critical. Ideally in the future, an individual will have a biomarker 'fingerprint', leading to a personalised combination of therapies. We are a way off that; this is the first step.

Ensuring patients make informed, considered choices

If and when approved, we will be discussing these treatments with many potential recipients, and applying strict criteria, at least initially. Many will be disappointed as ineligible and will need support. Those that are eligible need to understand a more complex picture than has been presented to a newly diagnosed patient until now. First and foremost, we must be clear with our patients on the likely effects of these initial drugs, and on the risks of taking them: ARIA will need careful discussion as will the ethical considerations around genetic testing for risk factors such as apoE status: professional training on these discussion points will be critical.

What do policy makers need to do to build on this success?

The sad fact is that if the drug was made available right now, very few centres in the UK, indeed across the world, would be able to give it safely and effectively. Memory services are

fragmented and under-resourced. They operate primarily on a community-based, palliative level with very few centres equipped to care for individuals having intravenous infusions every 2 to 4 weeks with regular monitoring for potential side effects.

We need a radical overhaul of our services, moving from support for a terminal disease towards active management of a chronic disease. Policy makers need to urgently engage with clinicians across the specialties involved in dementia care and devise a pathway that enables safe, appropriate provision of these (and other upcoming) drugs. Given the lack of staff, space, and diagnostics, this will require new ways of working and a collaborative networked approach, building bridges not castles.

Changing the Culture in the Real World

We must reframe our thinking on dementia so that professionals and public alike understand 'dementia' is the end stage of multiple diseases. The word is still stigmatised, associated with loss of person and dignity: until we shift thinking earlier to 'brain health' and risk management, with information tailored to pathology specific diagnoses, people will continue to shy away from a diagnosis. Working with other specialties e.g. stroke to develop a public campaign for brain health and the need for early diagnosis is critical.

Once symptomatic, patient selection for treatment will be challenging, as it will need biomarker confirmed diagnosis and rigorous eligibility determination. Given the patchy access to current diagnostic and monitoring tests, we will need nimble collaborative pathways to ensure the right people are channelled promptly for assessment and ongoing management. We will need to develop a pathway for patients with mild cognitive impairment – the group at highest likelihood of benefit from these drugs are currently not regularly seen in services.

As a triallist, I am acutely aware of the level of resource that goes into running a trial for a DMT. That is not feasible in the real world in terms of infrastructure, staffing, capacity for treatment and imaging. In addition, the level of control in a trial is very different to the 'messy' real world. Data collection from those who are clinically treated is critical to build a repository of knowledge on effects and side effects, enabling us to continuously improve determination of when and when not to give these drugs. To ensure successful roll out, we need to start with experienced sites with resource and build a service network, upskilling centres to provide tests such

as lumbar punctures, while validating scaleable systems for triage and monitoring. Others have been here before – MS; stroke for example. We can learn from the changes they had to make to services, and how the first drugs led to continuous improvement over the following years. Finally, ensuring we don't create a tiered system where those on drug get better care than those not on drug is vital – psychological, medical, and social care need to be enhanced to that end.

At the moment, most of the expense in dementia care is at the end stage, in social support. We need to 'level up' – we must put more resources into prevention, risk stratification, early diagnosis, and appropriate treatment in order to improve outcomes. We need to square the circle of how to improve resource in early stages, without reducing resource to support those unable to benefit from treatments in later stages.

It is critical that we don't wait until the treatment is approved to start making these improvements. Wholesale changes in services take time; the risks of waiting are exemplified by the difficulties implementing treatment with nusinersen in spinal muscular atrophy. It has been challenging managing patients with no treatments; it would be a tragedy if we finally have treatments that can make a difference but are not able to deliver them. If our policy makers grasp the nettle and invest in change now, we will all reap dividends in years to come.

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sporadic Alzheimer's disease (AD) and genetic forms of AD and frontotemporal dementia, including immunotherapies against amyloid and tau, and novel mechanisms in first in human trials including checkpoint inhibitors, gene silencing and AAV genetic therapies.

As clinical lead for the UCL Neurogenetic Therapies Programme, she has led a programme of innovative collaboration between industry and academia, developing novel biomarkers in a trial of a genetic therapy and introducing new methods to measure real time change in protein production/clearance in a gene silencing trial. Alongside her clinical work as Head of the cognitive service at NHNN, she was until recently the deputy chair of the NHSE Neuroscience Clinical Reference Group and chair of the Association of British Neurologists Services Committee, leading neurology service development and support in the UK. She is a member of the Alzheimer's Research UK taskforce, dedicated to raising awareness of dementia and reducing barriers to early and accurate diagnosis, and access to potential treatments.

There's everything to gain by not allowing the disease-modifying treatment tail to wag the dementia dog

Sube Banerjee

It is unequivocally great news that we are now seeing the first generation of disease modifying treatments (DMT) for Alzheimer's disease (AD) coming to market. This is a powerful proof of concept that drug treatment can work and will serve to invigorate efforts to generate cleaner, more powerful medications across the wide spectrum of aetiology of dementia. What these DMT will not do is abolish the immense personal, familial, and societal impacts of dementia. They are a partial answer to one specific question in AD, they are not the answer to dementia.

There is understandable enthusiasm from the pharmaceutical industry and some researchers to see diagnosis and care pathways from the viewpoint of the delivery of such medication. It is also true that, outside a few specialist centres, services are not currently constructed to carry out the necessary biomarker-based triaging of cases into treatment. Neither are they set up to monitor them for serious adverse events needed to enable the deployment of DMT in any meaningful way into clinical practice. Major change would be needed to deliver them, even in those jurisdictions where their costs might be borne.

The challenge is that the systems of dementia diagnosis and care which are being asked to respond are almost universally still patchy, of poor quality, and thinly resourced. Since dementia emerged as one of major health and care priorities a decade and a half ago, we have done great work in the relatively discrete domains of raising public and professional awareness of dementia, in increasing diagnosis rates, and in advancing research. We have been much less successful in the critical and more complex areas of building the services that are needed to ensure that all with dementia get: (i) an early and accurate diagnosis of what is causing the dementia; (ii) a clear care and treatment plan at that diagnosis; and (iii) good quality person-centred help, care, and support from diagnosis through the course of their illness to the end of life.

It is potentially informative to consider why we have done so much in some areas and so little in others. Primarily this is a failure of policy and strategy. The acknowledgment of dementia as a major health challenge that needed to be addressed on human and economic terms by the G7 in 2013 was a great step forward. However the unforeseen consequence of the communication and action of G7 members was that the eye-catching commitment to developing DMT by 2025 appears to have eclipsed the other, and potentially much more immediately and enduringly valuable, agenda of improving care and services. In a competition with the magic promise of drugs to make it all go away, all other actions were effectively deprioritised or forgotten.

We are in danger of doing something similar in the sphere of diagnosis by swallowing the line that a simple set of, as yet largely undeveloped (and untested in population samples), fluid biomarkers will make the diagnosis of AD and other subtypes of dementia for us. Why invest in services when we will have a simple blood test that will do it for us tomorrow? Well, because it won't. We need clinical pathways for people with cognitive concerns to enter which identify when they have the syndrome of dementia, what is causing it, and then help them. We should avoid "solutions" that effectively apply one test, and then tell people who are negative that there is no treatment for them.

Defeating dementia is a bold and noble cause. If it is going to mean anything for people with dementia it is also a complex not a simple challenge. HL Menken is reputed to have originated the aphorism that "for every complex problem there is an answer that is clear, simple and wrong". Delivering DMT is not wrong, but it is not enough. Delivering biomarker aided diagnoses of AD is not wrong, but it is not enough. Dementia is a complex challenge not a simple one, and we need strategy and action that is not afraid to engage with this complexity, that is multifaceted and seeks to change and improve the things that are difficult to do as well as those that seem simple to achieve. We need to deliver psychosocial care and support for the many not just DMT for the few.

The opportunity for health and economic gain by providing good dementia diagnosis, treatment and care comes from just how common and costly it is, and how we have not yet optimised systems to prevent harms and costs (such as preventable hospitalisation and unnecessary transitions into care homes). Playing a zero-sum game and taking what little

dementia has now to provide these first generation DMTs is the tail wagging the dog so that the dog falls over. It's like hanging a Picasso on the wall of a cottage where the roof has never been built and the windows are yet to be fitted. We must take the opportunity of the attention again afforded to dementia as a chance to build the roof of the cottage, fit those windows, and maybe even equip the kitchen, bathroom, and bedrooms so that people can thrive inside.

There is a huge amount that policy makers can do by commissioning case finding, good quality diagnosis (independent of fluid and other biomarkers), support and non-drug care and treatments that would enable people with dementia and their families to live their best lives with dementia. Good quality diagnosis, care planning and tailored post-diagnostic support can enable the prevention of harm, treating neuropsychiatric symptoms, preventing harm, and promoting good quality of life for people with dementia and family carers. The problem we have now is not that we do not have treatments that work, the problem is that we do not commission or provide services that deliver them at scale to all that would benefit from them.

With will, we could already provide great care for people with dementia, yet for vast majority we do not, there is a familiar postcode lottery within and between countries that means that almost nobody gets good quality care from diagnosis through to end of life. It is the family carers of those with dementia as well as those with dementia themselves who bear the human cost. It is governments and their health systems that bear much of the economic cost. We can defeat dementia by providing comprehensive dementia assessment and care. That would help with demand strains on primary care, general hospitals, home care, and care homes. It would reduce pressure on beds and enable timely discharge. Many of the challenges of our post-COVID health systems are in fact dementia shaped, whether the system recognises that or not, and it is dementia-shaped solutions that we need to meet them. We need to reject counsels of despair that say that such re-engineering of systems is too costly or too complex. It is inaction that is too costly. We should embrace the challenge of complex multifaceted answers to complex problems that deliver real solutions for dementia. We must not accept the false dichotomy of either DMT or great care, but embrace both, with that together we can defeat dementia!

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Personal Perspective on Timely Diagnosis in the era of emerging disease-modifying treatments for Alzheimer's Disease

Jetske van der Schaar

From syndrome to disease

For over a century, what we think of as 'dementia' has been defined as a syndrome that robs our loved ones of their abilities, their identity, and their lives. Despite the overwhelming number of 55 million patients worldwide,¹ until recently the cause of death could only be confirmed by autopsy. However, decades of research have taught us that the amyloid plaques and tau tangles characteristic of Alzheimer's Disease (AD), start accumulating 20-30 years before the onset of cognitive decline.² These pathophysiological changes can be detected increasingly early, reliably, and affordably by brain scans, in cerebrospinal fluid and even blood. This has led to a shift from a clinical to a biological diagnosis of AD, which is no longer based on signs and symptoms alone but supported by abnormal biomarker values, similar to common practice in oncology.³

Tipping the scales

This development has sparked a heated debate. Is it ethically acceptable to diagnose AD in patients when symptoms are still subtle or mild?⁴ The insight offers them a chance to improve their health, shift priorities in life and prepare for the future. Yet the prospect of developing dementia also poses a risk of emotional burden, stigma and discrimination. While clinicians have a duty to provide good care, patients have right to (not) know their test results. In the absence of an opportunity to stop, slow or prevent their dreadful future from unfolding, it has been considered harmful to label such persons as 'patients-in-waiting'. But encouraging results in multi-modal lifestyle interventions and recent breakthroughs in the development disease-modifying therapies have tipped the scales. Clinical trials with aducanumab, lecanemab and donanemab have shown to reduce cognitive decline in early stages of AD by respectively 29%, 27% and 29%,⁵ delaying disease progression by over five months compared to placebo in a timeframe of one and a half years.⁶

A new era

These results have heralded a **new era** in which AD becomes a treatable disease. The first drugs have received (accelerated) approval by the FDA and have been submitted for marketing authorization in Europe and Asia. This generation of medicines is certainly not a panacea but similar to developments in the treatment of Multiple sclerosis (MS), it will hopefully be ground-breaking for the introduction of more and better therapies for various causes of dementia. These advancements are revolutionizing the scientific field and will transform clinical practice over the next few decades. Given the potential to slow disease progression in early stages, individuals will have to be diagnosed timely in order to be treated. This will introduce new opportunities and challenges.

Predementia prevalence

On a global scale it is estimated that 32 million persons have dementia due to AD, meaning the disease has progressed to interfere with daily living on several domains, 69 million have prodromal AD, also known as mild cognitive impairment (MCI), which still allows them to function independently, whereas over 300 million have preclinical AD, indicating that pathology is present but no symptoms are detectable yet.^{7,8} It is unknown whether every individual at the beginning of the continuum will inevitably deteriorate and progress towards the phase of dementia. Nevertheless, a large proportion of patients are diagnosed in a late stage, when brain damage is so extensive it cannot be restored, whereas earlier stages offer a window of opportunity for preventive action by multi-domain lifestyle interventions and disease-modifying therapies.⁹ Even small delays in progression of the disease and onset of dementia would allow patients to live independently for a longer period of time, reduce the prevalence of dementia, and ease the individual and socioeconomic burden.^{10,11} Thus, it is critical to facilitate a timely diagnosis and treatment.

Contextualization

Given the numbers of patients, the resources involved and the already over-burdened health-care system, it is essential to contextualize the discussion on the timeliness of a diagnosis. The question of when to diagnose and whether to treat patients is difficult, if not impossible, to answer without context. Widespread population screening is different from conducting tests in individuals who visit a general practitioner or memory clinic because they have concerns or complaints. And even then, the case of an 83-year-old pensioner with comorbidities is distinct from a 59-year-old pilot flying passenger planes. The evaluation of costs and benefits is

dependent on the situation. Therefore, rather than designing a one-size-fits-all approach for all of predementia patients at once, policies and guidelines will have to be developed to allow a phased implementation, prioritizing those for whom a diagnosis may have the most personal actionability and medical utility. This will have implications in a clinical, personal and societal context, which I will describe next.

Figure 1 Patient journey of the future.

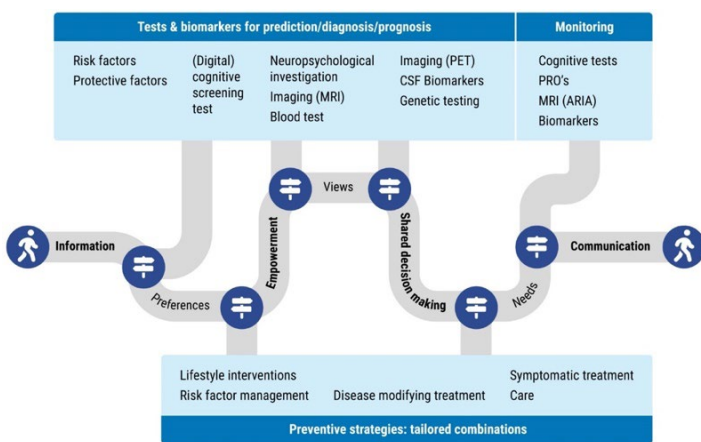


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Clinical implications

Memory clinic professionals, neurologists and geriatricians as well as general practitioners will have to be trained in (blood based) biomarker testing, interpretation of results and disclosure of the diagnosis. To facilitate this, standardized processes and materials need to be made available, when possible, supported by e-tools. A personalized approach with shared decision-making is recommended, to best align the provided care with patients’ preferences and needs (Figure 1). Some individuals may choose to remain unknown in ‘blissful ignorance’ for as long as possible, until symptoms interfere too much with their wellbeing or daily life. Others may opt to know ‘what lies ahead’ as early as they can, to explore all options for preventive action, including a risk-reducing lifestyle, disease-modifying treatments, and trial participation.

Personal implications

Detecting the presence of AD pathology before the onset of dementia is a sensitive matter, as it not only affects the body but more so the mind, with unique implications for patient’s identity and agency, as perceived by themselves and others. The insight is feared to evoke adverse emotions, such as anxiety, depression, or suicidal ideation, although empirical

evidence suggests an early diagnosis is well-tolerated and safe.¹² While it can be hard to live with an uncertain prognosis, a diagnosis can also offer an explanation for concerns, an incentive to arrange personal affairs, as well as an opportunity to adopt a risk-reducing lifestyle, participate in clinical trials, or receive disease-modifying therapy. Studies indicate that members of the general population are highly interested to learn whether they are in early stages of AD, and they believe this information is actionable. Still, similar to presymptomatic testing for other neurodegenerative diseases, the actual uptake may be lower than hypothetical willingness.¹³ In addition, it should be noted that excluding AD may be of even greater value. Patients need to be counselled on the possibilities and implications of predementia testing for AD in order to make an informed and deliberate decision. As considerations pro and con are specific to individuals’ characteristics and their circumstances, whether and when a diagnosis is timely may be very personal.

Societal implications

It is hard to grasp what it means to have a condition with subtle symptoms and an uncertain prognosis, especially as the definition of ‘alzheimer’s’ is changing in science and medicine but remains synonymous to ‘dementia’ among the general population. Persons diagnosed with AD in early stages may suffer from stigma, ranging from patronizing attitudes to social distancing, exclusion, and isolation, which may be internalized as feelings of shame or inferiority. Moreover, they may be vulnerable to discrimination, in their professional, financial, legal, and civil capacity. As current legislation does not adequately protect individuals who have AD but no dementia (yet), additional policies and legislation are required. Furthermore, it is important to make testing accessible and affordable for all individuals, regardless of race, ethnicity or socioeconomical status.⁴ Ultimately, timely detection and delayed progression can advance the development of better treatments, and lower the emotional, financial, and societal burden by enabling patients to participate in society, and live independently for a longer period of time.⁴ Therefore, it is vital to engage, educate and empower the general public, to improve awareness and attitudes, to mitigate adverse consequences, and to maximize favourable effects.

Timely preparation

For too long a diagnosis of AD has equalled a death sentence. Our generation is privileged to witness a watershed moment: for the first time in history, treatments are

becoming available that can offer time and quality of life to both patients and their loved ones. From now on, timely detection presents an opportunity to delay the onset of dementia, by adopting a risk-reducing lifestyle or receiving disease-modifying therapies. We have a moral obligation to inform the general public of pertinent information, to allow individuals to decide when testing is 'timely' for them, to enable at-risk persons to take preventive action and to offer treatment to patients who are eligible. The diagnostic tools are valid. The therapies are effective. What we need is a force of will, to set the wheels in motion and to start now.

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