Ministry of Health, Welfare and Sport

Defeating dementia

ESSAYS
Volume 1

Working together for health, wellbeing and resilience

Contents

Foreword
Conny Helder
Minister for Long-Term Care and Sport
The Netherlands

There are over 55 million people around the world living with dementia. As our societies age, their numbers will only increase – a slow and silent crisis that rarely makes the news headlines.
We might feel helpless in the face of this crisis. We have no means as yet to slow down or halt the disease, let alone cure it. And today's science can't even answer all the questions about why and how dementia develops.

So what we need is research. In the Netherlands we will double our national research budget over the next decade. And we will also have to double up our efforts. It's important that we do this together, because the only way to make real progress is by joining forces internationally, through increased funding, partnerships and innovation.

In the meantime, we must do our best to take care of those suffering from this cruel disease. They deserve good quality care, preferably in the comfort of their own home. This will help lighten the burden on our health budgets. And it will help people with dementia stay connected with society. Technology also allows us to take an extra step in improving care and support. Not to replace humans in the care system, but to enable people with dementia to live more independently and in a safe environment.

Still, we are not where we should be. WHO member states are far from reaching the 2025 national policy goals set out in the 'Global action plan on public health response to dementia'. We are seeing a decrease in government attention to dementia, a situation exacerbated by the COVID-19 pandemic, at a time when more and more people are living with the condition.

We want to renew international awareness of dementia and put the people who suffer from it back in the spotlight. To achieve this, the Dutch Ministry of Health, Welfare and Sport, in collaboration with the World Dementia Council, will organise a high-level conference on dementia in 2023. The aim of this conference is to agree on solid actions to improve dementia care and boost global investment in dementia research. In preparation for this event we will organise an online meeting to discuss some of the key themes that the conference will address.

This collection of essays is also essential in preparing for both meetings. In them, global experts discuss various science- and policy-related issues in the field of dementia and shed light on the challenges we face.

I would like to thank all the contributors to this publication for their work. I hope that you, the reader, will be inspired by this book. And that it will lead to inspiring conversations and actions that will help us meet our ultimate goal: curing dementia.

Introduction
Philip Scheltens

I am delighted to introduce and contribute to this collection of essays released ahead of a meeting the Netherlands government are organizing on dementia. The World Dementia Council is pleased to help organize the meeting.
Over the last year the Council has hosted a dozen global dialogues for international experts along with virtual and in-person wider meetings. Over 500 international leaders have participated, and I thank them all for their time. The dialogues covered different aspects of research, prevention and care.
On the first of those, this meeting comes at an exciting time for the field in the search for a disease modifying treatment. The year began with, shall we say, a high-octane debate around Aducanumab. This fall we have had the positive top line read out from the Lecanemab trial. No one is suggesting we have a cure here. We await the detailed data this November, but this is potentially a huge moment for the field and more importantly for patients and their families.
It is not though an unexpected moment for the field. For all the debate at the start of this year, it has always been a question of when, not if, over this decade we see disease modifying treatments in the clinic. And that has because the accelerating accumulation of knowledge over the last couple of decades. From tracers to blood biomarkers, we have made advances that have helped, and important will help, drive progress.

Fundamental to all of this has been the increases in funding we have seen for dementia research. We should not rest. Yes, funding has been increased, particularly in the United States, but relative to the scale of the problem, dementia research remains underfunded.
This collection of essays primarily focussed on the research agenda; it is but one aspect of the dementia challenge. The World Dementia Council's dialogues and discussion of the last year have addressed prevention. The best treatment for dementia is, obviously, not developing dementia in the first place. The last decade has seen the accumulation of evidence that, unsurprisingly, lifestyle impacts on your chances of developing dementia. There are modifiable risk factors that range from air pollution through to diet. But many of these risk factors are not dementia specific. Policy makers reducing air pollution or increasing childhood education has across the board benefits. There are good reasons to manage hypertension and diabetes. And if you smoke it is time to stop.

Where potentially there is more dementia specific potential is whether in discreet at-risk populations there are lifestyle interventions of some kind that change the risk of an individual developing dementia. There have been exciting studies and there are interesting models being implemented and pieces of technology being marketed. As we learn more, and understand better the science that underpins interventions, we can have greater confidence in the case for deploying a prevention strategy on scale.

A third topic we have addressed is care. The cost of providing care for ageing societies is a challenge governments around the world are grappling with. Countries are already facing significant cost pressures to deliver existing care provision. Families are meeting significant costs themselves. There are good models of person-centred care, good evidence base care intervention across multiple settings. And, of course, there is excellent provision and many dedicated people working in the sector or indeed providing care informally. Care provision has improved. But fundamentally limited funding for ageing care impacts on the quality of care that can be delivered.
Technology has potential to prove a major enhancer of the care offer but realising that potential, at scale, is some way off. There is huge potential to enhance the collection of data that would give a much richer understanding of quality of life and living with dementia.
We make progress. In research, prevention and care. Sometimes frustratingly slowly. And sometimes it doesn't feel like we are making progress at all. But we are. The question we should ask as a community is how we can do more? But we should also address where we need policy makers and governments to step in and work with us to improve the lives of people living with dementia and their caregivers now and in the future.

Professor Dr **Philip Scheltens** studied at the VU University Amsterdam, Netherlands, gaining his MD in 1984, and PhD (Magnetic Resonance Imaging in Alzheimer's disease) in 1993. In 2000 he becameProfessor of Cognitive Neurology and founded the Alzheimer Center at Amsterdam University Medical Centers, which he directed until 2022. His main clinical and research interests are Alzheimer's disease, vascular dementia, frontotemporal dementia, magnetic resonance imaging, PET imaging and fluid biomarkers. He is active in the field of biomarkers and clinical trials and has been the national PI for many studies, including phase 1-3 multicenter clinical trials. He supervised 100 PhD theses. In 2013, he co-founded the Dutch national plan against dementia (Deltaplan Dementie) and served as chair of the board UNTIL 2020. He has authored over 1100 peer reviewed publications and his H-factor is currently 113. In 2011, he was elected as member of the Royal Dutch Academy of Arts and Sciences (KNAW) and serveD as Secretary General UNTIL 2020. In 2016. he was awarded the European Grand Prix for Alzheimer's Research. Since 2020. he gradually moved into a new position as Head of the Dementia Fund at EQT Life Sciences. In 2021, he was appointed Chair of the World Dementia Council.

Some dementia reflections
Sir Dennis Gillings

It is encouraging to see the recent progress on dementia that has taken place since London's groundbreaking G8 Dementia Summit in December 2013. At the same time, overall progress towards an end point of more efficacious treatments is limited. Moreover, ever increasing numbers of questions about dementia, in all its forms, sit squarely on the table. Such is the nature of a multi-faceted, evolving condition of an extraordinarily complex organ, namely the brain.

Committed government leadership by David Cameron, then UK Prime Minister, continued following the 2013 summit. This set in motion much more widespread attention to dementia and, in turn, increased societal discussion, research investment and frequency of media coverage. The World Dementia Council was formed in 2014 under UK leadership to provide an international platform for goal setting, policy alternatives, improved data, disease care options, efficacious treatments, and regulatory actions. UK Government leadership was very critical during these initial stages as several influential doors and networks were opened to the World Dementia Council across the EU, USA, Canada, Australia, Japan, multiple embassies and WHO to name but a few.

As the G8 (becoming the G7) sponsor, UK government materially increased dementia related funding. US financing of dementia research increased even more substantially, with increases continuing to this day, through the support of a sympathetic Congress. WHO generously hosted a highly attended conference in 2015 of health leaders from all over the world to widen geographically the focus on dementia.

It is true that efficacious treatments for dementia have not yet made the progress that was talked about back in 2013. However, the verdict is still out regarding achieving the original goal of a curative therapy by 2025. At the time of writing this article, it is reported that Lecanemab is achieving statistically significant clinical benefit by reducing cognitive decline. At least two other broadly comparable pharmaceutical treatments are in Phase 3 clinical trials.

Regardless of the timing of therapeutic advances, much additional ground has been gained in the dementia battle. The multiplicity of disease mechanisms, genetic effects, lifestyles, and environmental conditions that lead to dementia are being dissected with increasing scientific clarity. Well-funded brain science is progressing exponentially and will likely unravel over this decade much of the complexity of underlying molecular mechanisms that take place during brain functions. Both the disentanglement of disease processes and a fuller understanding of the brain will be needed if we are to conquer dementia in some or possibly all its forms.

The example of cancer can be extremely helpful to understand the broad path that dementia therapy is likely to take. It is now fully agreed that cancer has multiple underlying disease mechanisms, but this was far less clear 40 years ago. Many of these mechanisms are now partially or fully understood and this has moved cancer treatment to a new era that is delivering continued improvements in patient longevity and quality of life. Many different therapies are usually involved treating cancer patients and this will also be the future for dementia.

The economic impact of dementia deserves mention. It is substantial and likely to grow into a huge financial drag at both the individual or family level and at the population level. Dementia usually becomes noticeable during later years and progresses relentlessly impacting quality of life and independence for as many as 1-2 decades. Moreover, the tragedy of early onset, often through genetic inheritance, is also a devastating reality for some. Dementia typically requires expensive long-term care in its middle to later stages together with family and/or community support. These factors compound to generate ever increasing societal costs as populations age. The projected economic and family impacts will be daunting as the 2030's unfold unless more efficacious therapies that have real impact become available and reduce the incidence of new cases.
More attention is being paid to preventive measures such as new learning in later years, appropriate physical activity, good nutrition, and sensible lifestyle choices. Prevention has promise but may have limited population impact unless serious public health education efforts are undertaken.

It is good news that the biopharmaceutical industry is increasing its investment in dementia and broadening this investment far beyond the previous, almost universal, focus on amyloid removal. Again, this follows the progression of cancer treatment which was historically dominated by chemotherapy but has now widened to a degree that would not have been recognizable a generation ago.

High quality care of subjects with dementia related problems is expensive, as previously stated, and requires serious health policy attention. Families affected can face almost impossible demands on their busy and complex lifestyles. There are models of high-quality community care that are successful in terms of individual comfort and wellbeing, but the corresponding expense does not allow governments the financial freedom to provide uniform support across society. Digital connectivity used effectively will enable costs to be reduced but not by a sufficient margin to enable adequate care across large populations unless therapeutic advances reduce dementia incidence. It is not acceptable for future longevity advances that seem likely to occur to become offset by quality-of-life reductions. To some extent this has already happened over the past few decades.

Our research scientists will be able to prevent this conundrum as long as adequate and consistent funding is dedicated to dementia in all its forms. The current brain science impetus and broader therapeutic testing must be maintained and, perhaps, increased if we are to achieve the win-win of greater longevity with high quality. Leadership and financial support from government to achieve this will continue to be as important as it was in galvanizing a focus on dementia back in 2013.

Sir **Dennis Gillings** CBE, FMedSci, is co-founder and former CEO and Executive Chairman of Quintiles which merged with IMS in 2016 and is now IQVIA. Dennis served on the IQVIA Board as Lead Director until retiring in 2018. In 2014, Dennis was appointed World Dementia Envoy by former UK Prime Minister David Cameron. In this capacity, Dennis helped found and became first Chairman of the World Dementia Council, an organization that seeks to reduce cognitive decline. In particular, as Envoy, he worked with governments and major institutions to provide leadership to address economic, regulatory, and social barriers to the prevention, treatment and care of dementia.

Prior to founding Quintiles, Dennis was a Professor of Biostatistics at the School of Public Health (now the Gillings School of Global Public Health) at the University of North Carolina at Chapel Hill. Among many honors he has received, Dennis was awarded the Commander of the Most Excellent Order of the British Empire in 2004 for services to the pharmaceutical industry and was knighted in 2020 for services to the advancement of dementia and life sciences research. He has received fellowships and honorary doctoral degrees from several institutions including UNC Chapel Hill, University of Southampton, UCL, Kings College, Queen Mary, Exeter University and The UK Academy of Medical Sciences recognizing his academic and commercial contributions to the life sciences.

Dementia: Time to Act
Bart de Strooper

Dementia is not waiting. In the UK only, an estimated 944k people live with dementia, a figure expected to rise to more than 1 million by 2030 and 1.5 million by 2050. Globally, the number of people with dementia will increase by more than 200 percent, from 50 million in 2018 to 152 million by 2050. We are in a race against time to predict who is at the greatest risk of developing dementia, how to prevent it, how to diagnose it early, and how to intervene.

Dementia is not a disease. It is merely a (very late) symptom of the end stage of different neurodegenerative disorders which start decades before cognitive decline manifests. These disorders are complex, and we still face a huge knowledge gap in understanding them. Just think - although the number of people with dementia and cancer are similar, cancer research is funded tenfold more – and this is reflected in the daunting difference in publications (about 250k in dementia, more than 4.5 million in cancer), number of clinical trials and available drugs.

Massive investment in cancer research over the past decades has been crucial to develop effective therapies with huge impact on global health. Urgent investment of resources to tackle the Covid challenge led to over 137k publications in *just 3 years,* matching the amount of papers published in the Alzheimer's field over *a century* and delivering effective vaccines and treatments. This is what getting serious about a health challenge looks like. Everything starts with strong and stable investment in basic research, which then fuels the pipeline towards discovery and medication. While in a hurry to get to a cure, sometimes our field seems to forget this simple truth.

First, we need a better definition of what we are studying by a better and earlier diagnosis of the disorders that cause dementia. We need cheaper tests such as blood biomarkers, and more functional tests such as computer games combined with direct measurement of brain function. Clinicians should move away from the late dementia stages and try to detect earlier signs of neurodegeneration, which can be objectivised with those tests. This will lead to a more rational approach to dementia diagnosis and will provide the testbed for interventions, new treatments and research into the early phase of disease.

Second, we need to empower the people with dementia and their caretakers by providing them access to better diagnosis. This will inform people very early on their condition, when they have still the potential to make decisions for themselves. One very hopeful evolution is the increasing availability of technologies allowing those living with dementia to stay longer at home. Real-time monitoring combined with artificial intelligence and feedback to health professionals will lead to efficient and targeted intervention. Investment in such teams and technology systems could lead to huge savings by lowering the number of people hospitalised with dementia (now occupying 25% of hospital beds in the UK).

Third, we need ambitious research and drug development. Better diagnosis and better care are only sustainable if we also work on fundamental solutions. Research should dive deep and focus on early mechanisms of disease. The future treatment of disorders leading to dementia will need polypharmacy (the analogy with cancer is clear). This part of the strategy needs close collaboration with industry and clinical trialists. Every patient should be offered the chance to be included in ongoing clinical trials. We need new regulation regarding trials in this field.

Fourth, we need to embrace the revolution in data science. Our data scientists will be fed with massive amounts of high-quality data: diagnostics, symptoms, comorbidities, lifestyle, molecular and brain research, unsuccessful drug trials, etc... all will be used to build more adequate and comprehensive models of disease. We will find factors that can be controlled to reduce incidence of dementia and we will implement those in our public health services, collaborating with GPs, primary care and community practitioners.

With innovation transforming diagnosis, trials expanding access to many more people living with dementia, and advances in experimental approaches, technology, genetics and data science, there are certainly many reasons to be excited and hopeful. Only by investing in research, empowering scientists and helping them to think in a translational way we will truly accelerate the path to treatments. The recent promising results of Lecanemab show the way forward: persistence, belief in the science, and learning from previously failed trials will ultimately lead to a real breakthrough in the AD field. Many more will come.

In a post-pandemic world, the scale of the dementia challenge will increase even more. The wider dementia community needs to stand ready for this challenge, coordinating efforts across the clinical and research sectors and supported by government strong leadership in providing long-term, increased funding. We can no longer wait.

Bart De Strooper, MD, PhD is director of the Dementia research Institute of the UK and professor of molecular medicine at the VIB Centre for Brain and Disease research University of Leuven and Professor at University College London. His scientific work is focused on the understanding of the fundamental mechanisms that underlie Alzheimer's and Parkinson's disease. His major finding is the identification of gamma-secretase and its role in the proteolysis of the amyloid precursor protein and in Notch signaling, for which he received the Brain Prize 2018 together with Hardy, Goedert and Haass. Recently he has reoriented his work to the understanding of the cellular phase of Alzheimer's disease. His aim is to understand the mechanisms of resilience that make that some people survive into very old age with the biochemical signs of Alzheimer's Disease but without the symptoms of dementia. He has published close to 400 papers with h-index of 121 and is recognized as highly cited researcher 2018, 2019 and 2020 (Clarivate, Web of Science Group). Expertscape considers him World Expert in Alzheimer's disease (no 8 worldwide), Presenilins (no1 worldwide) and Amyloid beta- Peptides (no 4 worldwide).

Clinical Trial Infrastructure is Needed in All Countries

Jeffrey Cummings

Alzheimer's disease (AD) is an international challenge to public health and is increasing as the world's population ages[1] New therapies that prevent, delay the onset, slowed the progression, or improve the symptoms of AD are urgently needed. The development of new therapies for AD requires a global enterprise. All countries can participate in drug development, assist in solving the global challenge posed by AD, and evaluate the efficacy and safety of new therapies for their citizen-populations. There are many important reasons to develop the infrastructure for randomized clinical trials (RCT's) in nations around the world. (Table 1).

AD is a common disorder and is becoming more frequent with global aging. The high frequency of the disorder does not translate into ease of clinical trial recruitment. The advanced age of the patients, similarly advanced stage of the care partner, the presence of comorbid illnesses that may exclude the patient from participation, the prescription of drugs for comorbid conditions may exclude the patient from being included, and the demands of clinical trials including visits to the clinical trial site, brain imaging, blood sampling, neuropsychological testing for the participant, and questionnaire completion for the participant's care partner all reduce the rate at which patients can be entered into RCT's. The result is prolonged recruitment periods and delay in developing new therapies. More clinical trials sites are needed to recruit patients for trials and shorten recruitment times.

Development of RCT sites around the world can help resolve this recruitment challenge and accelerate drug development. RTC's provide critical efficacy and safety information for emerging therapeutics. RCTs provide the only type of evidence acceptable to most global regulatory bodies for approval of marketing in the countries to which their regulations apply. Inclusion of diverse multi-regional multi-national populations in RTCs is critical[2]. Citizens of all countries should have equity of opportunity to participate in research. RCTs are conducted before promising drugs are approved, are the only means of accessing emerging experimental therapies, and provide a conduit for altruistic impulses to help develop new treatments.

Table 1. Key reasons for global development of clinical trial infrastructure.

Provide equity for research participation across nations

Assess efficacy in regional populations
- Extrinsic factors that may affect efficacy assessments
  - Disease diagnostic standards
  - Medical care of the region
  - Commonly use concomitant medications
  - Diet and nutrition
  - Cultural or socioeconomic factors
  - Educational level of participants
  - Clinical trial site expertise
- Intrinsic factors that may affect efficacy
  - Participant body mass (may affect pharmacokinetics and pharmacodynamics)
  - Genetic polymorphisms that vary by race or ethnicity
  - Microbiome composition

Establish safety in regional populations

Create a knowledge base for the safe and effective use of emerging therapeutics in regional populations

Advance local understanding of Alzheimer's disease

Grow the nation's scientific workforce

Develop revenue streams to support the scientific infrastructure

Establish local infrastructure to support local biotechnology enterprises

Multi-national participation in RCTs is important for many scientific reasons. Global populations vary substantially in size, and dose choices may be influenced by this size of the participants involved. There are many intrinsic factors such as genetic influences on the metabolism of drugs as well as on biological aspects of transmitter receptors that may affect the pharmacokinetics and pharmacodynamics of therapies[3]. The impact of genetically distinct metabolic pathways can be discovered only with the multi-national populations in RCTs. Microbiome composition and the influence of the microbiome on drugs as well as the influence of drugs on the microbiome may vary among regions and nations. Extrinsic factors such as regional medical care and diagnostic standards, diet, educational level, and scientific expertise of the site staff may influence trials outcomes[3].

Building clinical trial infrastructure has many advantages for countries[4]. It allows the staff of the national clinical trial sites to participate in global drug development and enhance the scientific expertise of the nation's scientific community. RCTs advance the scientific understanding of the staff working in clinical trial sites and this knowledge diffuses to family and friends. Participation in global clinical trials may be a source of revenue that can assist in sustaining the national clinical trial infrastructure. The availability of clinical trial sites in a country allows local drug development and biotechnology companies to have a collaborative partner to test candidate therapies. Given the great need to develop new therapies for AD and the many advantages to a nation's citizens of being able to participate in RCTs, it is to the advantage of governments to extend themselves to develop RCT infrastructure.

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Jeffrey Cummings, MD, ScD, is Founding Director, Cleveland Clinic Lou Ruvo Center for Brain Health. He is the Joy Chambers- Grundy Professor of Brain Science, Vice Chair for Research, and Director of the Chambers- Gundy Center for Transformative Neuroscience, Department of Brain Health, School of Integrated Health Sciences, University of Nevada Las Vegas (UNLV). 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 ScienceTM."

Historic momentum in treatment and research Maria Carrillo

We are living in historic times for Alzheimer's, this decade will be remembered as the decade that gave us the next hope for changing the underlying biology of Alzheimer's disease and slowing a person's decline. A report of positive results in Alzheimer's disease clinical trials was reported recently, giving those facing Alzheimer's incredible hope for more effective treatments.

The topline data reported last month indicate a positive result from the closely-watched clinical trial of lecanemab, an anti-amyloid monoclonal antibody for the treatment of mild cognitive impairment (MCI) due to Alzheimer's disease and mild Alzheimer's dementia. We are enthusiastically looking forward to the data behind the readout later this year. On behalf of all people affected by Alzheimer's disease around the globe, we are energized about the announcement and the future for more effective treatments.
(Read our statement here).

Funding and philanthropic support fueled this momentum
Seeds planted years ago by researchers and policy advocates are starting to blossom as the number of potential treatments for Alzheimer's begins to grow.

At any given moment, research and discovery are happening. The Alzheimer's Association currently has more than $310 million active in over 950 projects in 48 countries, spanning 6 continents.

The effects of our public and private funding strategy are dynamic and essential. This is demonstrated by the actions of Alzheimer's Association and Alzheimer's Impact Movement (AIM), a separately incorporated advocacy affiliate of the Association, which activated the U.S. federal government to rise to the challenge. Thanks to relentless efforts of volunteer advocates, Alzheimer's and dementia research funding at the National Institutes of Health (NIH) has increased seven-fold in the last decade, from $100 million in 2011 to over $3.5 billion in 2022.

Investments from philanthropists have played a pivotal role in accelerating momentum. For example, in the last decade, Part the Cloud has raised $65 million to support 65 projects, which have gone on to secure $1 billion in follow-on funding from other funding sources including government, industry and venture capital.

Scientific discourse and healthy debate in the field
We recognize the positive and healthy debate among scientists around the best way to tackle this disease. It is clear that anti-amyloid approaches are not a "silver bullet," they are the first wave of treatments that address the underlying biology of Alzheimer's with potential for real benefits for people living with early-Alzheimer's and mild cognitive impairment. These results support the amyloid therapeutic hypothesis and the U.S. FDA accelerated approval on the basis of amyloid reduction.

Blood-based markers (BBMs) show promise for improving, and possibly even redefining, the diagnostic work-up for Alzheimer's. This progress is due in part to investments in workgroups like the Global Biomarker Standardization Consortium (GBSC) more than a decade ago gather key researchers, clinicians, industry, regulatory and government leaders in Alzheimer's disease and dementias to achieve consensus on the best ways to standardize and validate biomarker tests for use in global clinical practices. Remarkable progress has been made, but additional data are needed before BBMs can be used as a stand-alone test for diagnosis and considered for broad use in primary care settings. At the same time, they are important and valuable for current research trials and cautious initial use in specialized memory clinics.
The Alzheimer's Association has been laying the groundwork for this and funding these approaches for over a decade. Today, the growing Alzheimer's drug development pipeline is robust with a wide variety of treatment approaches, some of which will work effectively with anti-amyloid drugs in powerful combination therapies.

We must be committed to advancing all potential treatment avenues, and exploring methods for integrating diverse approaches into combination therapies. We remain steadfast in our commitment to advancing the science of Alzheimer's and dementia treatment, continue to diversify the treatment pipeline, and focus on all scientifically legitimate avenues of research.

Commitment to diversity of thought and supporting researchers everywhere, at all levels
And it's diversity of approaches, diversity of thought, and diversity and inclusion in our studies that will get us to the next milestone. We are committed to bringing new researchers to this field and supporting them through the Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment (ISTAART). And helping them stay here, with grants we award specifically to early-career researchers around the world. The International Research Grant Program focuses on funding researchers from underserved and underrepresented backgrounds and further examine the impact of the disease on diverse populations.

Convening the global research community during a pandemic is undoubtedly challenging, but it has offered us all unique opportunities. Alzheimer's Association International Conference® 2022 (AAIC®) took place as a hybrid meeting, gathering researchers from around to world at the largest dementia science conference to discuss the full breadth of research, including the basic biology of aging and the brain, risk factors and prevention strategies, caregiving and living well with the disease, and much more.

This winter, we are partnering with others to host the Dementia and Brain Aging in Low- and Middle-Income Countries (LMIC) conference in December in Nairobi, Kenya. ISTAART is further working to identify gaps in dementia care & research in LMICs, and has convened a working group of international scientists to focus on this effort.

We quickly learned that our ability to advance discussion and reach more scientists of all levels was greatly accelerated, due to shifting to virtual platforms. And with the unparalleled benefits of in-person convening and networking, hybrid meetings offer the best of both worlds – expansive reach, inclusion, and more diversity of thought and approaches. I am pleased to announce that AAIC23 will take place both virtually and in-person in Amsterdam next July.

Commitment to progress
While this is an inflection point, it is not a stopping point. Treatments that deliver benefits to people living with Alzheimer's disease are just as valuable as treatments that extend the lives of those with other terminal diseases.
This is history in the making. This is the time we will look back at and say, "that was when it all started." I am proud to be a part of this global community, fighting to end Alzheimer's and all other dementia.

As chief science officer, **Maria C. Carrillo**, Ph.D., sets the strategic vision for the Alzheimer's Association global research program. Under her leadership, the Association is the world's largest nonprofit funder of Alzheimer's research — investing more than $455 million since 1982 — and an internationally recognized pioneer in convening the dementia science community. Dr. Carrillo uses her platform as a noted public speaker to play an instrumental role in the Association's efforts to lobby for increased funding for the disease.
Dr. Carrillo oversees the implementation of the Association's growing portfolio of research initiatives, including the Alzheimer's Association International Conference® (AAIC®), the world's largest and most influential dementia science meeting, and the Research Roundtable, which enables international scientific, industry and government leaders to work together to overcome shared obstacles in Alzheimer's science and drug development. In addition, she leads the Association's direct involvement in research by serving as a co-primary investigator for the Association-funded and led U.S. POINTER study, a lifestyle intervention trial to prevent cognitive decline and dementia.
Dr. Carrillo earned her Ph.D. from Northwestern University's Institute for Neuroscience and completed a postdoctoral fellowship focused on Alzheimer's brain imaging and risk factors at Rush University Medical Center in Chicago.

JPND's role in facilitating brain health partnerships in Europe and its international strategy in expanding research partnerships without boundaries

Philippe Amouyel

The name JPND (EU Joint Programme - Neurodegenerative Disease Research) is synonymous to the largest global research initiative for Neurodegenerative Disease (ND) research in Europe and beyond. It is also known for promoting ND research without boundaries. Indeed, one of JPND's key objectives is to fortify its work in brain health partnerships in Europe, to better combat the challenges of ND and of Alzheimer's disease in particular. The economic and social challenges in facing these diseases will only continue to grow; therefore, it is crucial that there is alignment in ND research and partnerships towards brain health that will help address and alleviate the increasing societal and economic burdens of brain disorders.

What is JPND?

JPND's unique programme enables the 30 participating countries to collaborate on tackling the challenge of ND. JPND is a non-binding collaboration relying on trust among its members who engage voluntarily on a shared vision, a reactive management structure and a common Strategic Research and Innovation agenda (SRIA).

JPND supports highly competitive transnational collaborative projects that link research teams from several countries and by juxtaposing large national research grants. In doing so, JPND has created a virtual common pot that efficiently supports each team of researchers towards a shared objective.

JPND calls incentivise translational approaches associated with high-level basic research. However, as ND research is not limited to finding curative treatments, these chronic diseases also require other forms of support for both the patients and their caregivers. For this reason, JPND also strongly supports social and healthcare research and public and patient involvement.

JPND and Patient and Public Involvement

Another crucial component in JPND's move towards stronger brain health partnerships is to foster greater public and patient involvement (PPI) in brain health research. JPND has been calling for heightened awareness in the need to incorporate PPI in ND and brain health research. There is an overt call for the strategic implementation of PPI in JPND's annual calls, the encouragement of active PPI participation in all of JPND-supported projects, the training of public, patients and patient advocates, the running of workshops emphasising PPI, the acculturation of scientists and physicians to PPI and dedicated PPI pages on JPND's website to increase awareness of the important role PPI plays in brain health research.

JPND's international strategy

As a 30 member strong initiative, the investment in ND research through joint transnational calls has increased. As of now, the total investment is 190 million euros. With its annual transnational calls for research projects and its offer of research databases, JPND is now a reference for European and global knowledge and an innovation platform in the area of ND. Nearly all JPND member states have a national research strategy in ND. The Expert Center for Young-onset Dementia in the Netherlands, whose research agenda is based on the JPND Strategic Research and Innovation Agenda (SRIA), is testimony to the global outreach of JPND. The national dementia research programme of 2021-2030 in The Netherlands, with a total budget of over €150 million, is based on the JPND SRIA.

Moving forward, JPND plans to intensify bilateral contacts with various countries, focusing on their specific research capacities and connecting with their government's policies. JPND also leverages on available networks like the World Dementia Council (where JPND has a seat) to reach out to new contacts.

How can Europe address the challenges of brain health?

Europe can address the challenges of brain health by capitalising on existing international initiatives like JPND, facilitating access to infrastructure and resources, structuring brain research area, reinforcing patient and public involvement and accelerating research transfer and innovation. Amongst European brain health collaboratives, there is a need to strengthen collaborations between each one and to work towards establishing a common brain health agenda. In the last ten years, both the European Commission (EC) and its Member States (MS) have established and led initiatives in Europe to face these challenges collectively. To date, there is JPND, the largest global collaboration in this field/domain; NEURON – an EC ERANET partnership that supports basic, clinical and translational research in the fields of brain diseases and the Human Brain Project – an EC's Future and Emerging Technologies Flagship funded by the seventh framework programme that aims to put in place a unique Information and Communications Technology-based infrastructure for brain research. In 2019, together with the European Brain Council, these three initiatives began discussions in the context of an EU-funded European Brain Research Area (EBRA) EC Coordination and Support Action, to discover operational synergies, identify strengths and gaps and foster alignment across European and global brain initiatives.

A European Brain Research Area

In February 2022, EBRA released its long-awaited European Research Inventory and Mapping Report, providing insight into the brain research activities that are funded at the European level within the EU framework programmes FP7 and Horizon 2020 (the Framework Programme for Research and Innovation (2014-2020) under the ERA-Net Cofund programme), as well as the funding initiatives of JPND, ERA-NET NEURON and the Human Brain Project. The mapping report gives an overview of the current state of brain research in Europe and the areas of brain research (if any) that are being focused in Europe. The report shows that, in spite of increased support in brain research, funding is still lacking in all areas of brain research in the EU. More focus is needed on public and patient engagement and on enabling data sharing. From 2007 to 2019, the EC and leading European brain research initiatives allocated €6 billion to about 4,000 brain research projects, an average of €500 million per year. From 2008 to 2012, an average of 400 million was invested per year, increasing between 2014 to 2018 to 550 million, marking a steady growth.

However, continued funding of research consortia across countries is key for a lasting impact on collaboration and innovation in the European and global brain research area.

"It is now time to accelerate this momentum through an ambitious partnership on brain health in Horizon Europe under a coordinated approach." –

Philippe Amouyel, MD, PhD, chairs the EU Joint Programme on Neurodegenerative Diseases research (JPND), a 30-country led initiative, including Canada and Australia, aimed at tackling the challenge of neurodegenerative diseases, the largest global research collaboration in this field. JPND is a joint programming approach to research collaboration in Europe and beyond, bringing countries together to address challenges that are over the scope of any single nation. He is Professor of Epidemiology and Public Health at the University Hospital of Lille in France. He heads a large academic research unit working on public health and molecular epidemiology of aging diseases. His research is devoted to the study of determinants, mainly genetic, of Alzheimer's disease and to the prevention of cognitive decline. He participated in the discovery of more than 90% of the genetic susceptibility factors published in Alzheimer's disease. From 2002 to 2011, Philippe Amouyel headed Institut Pasteur de Lille. Since 2008, he has been the general director of Fondation Alzheimer, a private non-profit foundation dedicated to supporting innovative and cutting-edge research for Alzheimer's disease and related disorders that promotes the prevention of cognitive decline. Philippe Amouyel is member of the World Dementia Council for a global action against dementia.

Technology Enablement of Dementia Treatment, Care and Prevention

Rhoda Au

The World Health Organization's estimated number of dementia cases of 55 million today, 78 million by 2030 and 139 million by 2050 do not tell the whole story. They fail to capture the many more millions that will not be diagnosed because there are not currently appropriate diagnostic tools to do so or trained healthcare experts to use them. They fail to quantify the social burden not just on families, but also on the communities in which both the identified and the unidentified will reside within. They fail to capture the fear of not knowing what to do with a diagnosis or the problem of not even knowing what to fear. While there are many working to address the problem of diagnosis, care, treatment and enlightenment, there is one underlying concern that limits both the scope and scale of any of these solutions – the high resourced setting bias. Much of the work is led by people with access to resources that are not available to most others. Much of the work is done on people who live in higher income settings. The net result is diagnostic, care, treatment and enlightenment solutions that are well-tailored to a small proportion of the overall world population. For the rest of the world, the options have largely been to either adopt copy-cat approaches where direct translation and customization attenuate but do not eliminate the inherent bias built into these methods or to simply not do anything because the methods being promoted are just not feasible. The aspirational goal of eradicating dementia will never be met if the assumptions of what to do and how to do it are not reassessed.

The tipping point for changing the current trajectory is now. Technology has lowered the barriers for collecting data, which has resulted in an exponential increase in information gathering that continues to grow exponentially. Estimates are that 2.5M terabytes of data are generated every day. Statista reports 97 zetabytes of data in 2022 with projections of 181 zetabytes in 2025 (note there are one billion terabytes in one zettabyte). It begs the question of how on the one hand, technological advances are being used to gather, process and interpret data at an unrelenting pace and scale, yet on the other hand, we have a big data gap in the realm of dementia related information that is leading to distorted practices that are relevant to very few?

The Davos Alzheimer's Collaborative (DAC) has embraced the challenge of global underrepresentation by leveraging the power of technology to accelerate the discovery of treatment and care pathways for dementia. Additionally with a broader focus on brain health, DAC is also focused on finding the multi-factorial approaches to dementia prevention. These objectives combined provide the 3-pronged strategy (treatment, care, prevention) necessary to squelch this rapidly rising worldwide pandemic.

DAC's primary technological solution for filling the data gaps is through the smartphone. With over 6.6 billion people in possession of a smartphone today, these mobile devices contain all the sensors needed to collect digital data streams that can be converted to relevant measures needed to detect and monitor brain health. The smartphone also provides a communication network that allows development of low cost, but easily scalable "high touch" methods for on-going engagement. These interactions can include monitoring for symptoms that indicate increasing risk for dementia and/or for delivering care solutions and monitoring their impact in real time. For those with significant behavioural or physical impairment that require assistance, this communication network can link everyone on the healthcare team with family members and caretakers who are involved in the day-to-day care of the person with dementia.

Another major technological advance that is taking root are cloud-based interoperability platforms that are being built to process, house and make data accessible to scientific talent, independent of where they reside. This is important for several reasons. First, digital technologies applied to dementia/AD is still at a nascent stage. No digital assessment should be assumed to be at a point of sufficient maturity; there is far more to be gained from digital data than is currently known. Second, the lack of data access has created a muffled scientific voice, where only those with the greatest access to data are being heard. Third, scientific discovery can come from anyone, anywhere. Paradigmatic shifts are frequently sparked by new perspectives offered by those outside the field of inquiry because too much "group think" is being perpetuated by those within the field. But one considerable potential barrier that must be countered are interoperability platform silos. It is critical to put aside inherent protective instincts that lead to inappropriate concepts of data ownership. Data should be recognized as owned by only the person who gives it. Those creating interoperability platforms should understand they are simply stewards, responsible not only for protecting confidentiality of the data contributor, but also for accepting the obligation to ensure that it is used to the maximum benefit of science. This means every interoperability platform created should be linkable to all other interoperability platforms so no one dementia data resource sits in isolation. The National Institute on Aging within the U.S., along with the Alzheimer's Disease Data Initiative, are two examples of groups that are working to prevent interoperability data kingdoms that are currently in danger of preserving deep rooted data hording proclivities.

The final major technological advance that needs to be better harnessed universally are advanced data driven analytic methods being driven through data science and artificial intelligence. Longstanding research precedent is resulting in science that fits well-known and well-used methods at the expense of developing much more forward-thinking novel approached that will fit the actual scientific need. As any government official engaged in developing and enacting public policy knows, change is hard. And it is no different in the realm of dementia care and research. The resistance among clinician scientists to embrace the data science potential is slowing the progress toward clinical insights for treatment and care of people with dementia, including development of solutions that are outside the purview of the medical community's control.

Better convergence of public health and medical practice should be the result of any strategic vision for the treatment, care and prevention of dementia, including Alzheimer's disease and related disorders. Technology available today can enable having the right data on the right people made accessible to the right mix of diversity of skills. The question should not be whether this can be done but rather should be on how quickly to do so.

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The need to advance dementia research globally

Ren Minghui,
Soumya Swaimanthan

Dementia is one of the greatest health challenges of our generation. Currently, over 55 million people live with dementia globally (1). With an expected increase to 78 million by the end of this decade, dementia is set to overwhelm health systems, care infrastructure and economies worldwide. Alarmingly, with over 60% of people with dementia living in low- and middle-income countries (LMICs), where the largest rise in dementia cases is expected in coming decades, current health and social care systems are unprepared to deal with such an impact. This is despite international commitments made during the 2013 G8 dementia summit, reinforced by the adoption of the Global action plan on the public health response to dementia 2017-2025 (2), and the Okayama Declaration of the G20 Health Ministers in 2019.

To this end it is imperative that research becomes an integral part of the global dementia response. Notwithstanding the many scientific advances, there is still no cure for dementia. In many ways, our understanding remains limited to how to prevent and treat the underlying causes of dementia and provide good quality care and support for people with dementia and their carers. We must therefore ensure that all aspects of research such as basic science, clinical research, and implementation science as well as the critical areas across the dementia care pathway including risk reduction, diagnosis, treatment, care, and rehabilitation are adequately addressed. Overall, dementia research often remains uncoordinated, leading to diverging approaches and unnecessary redundancies. This fragmentation also contributes to a great disparity and variability in research investment and quality.

Despite recent boosts in dementia investment in some countries, research funding overall is still not proportionate to the impact and societal cost of dementia. Moreover, with most funding originating from, and directed at, high-income countries, LMICs have had little voice in decision making and are vastly underrepresented in global dementia research landscape. Of the 50 organizations and institutions that received the most grants for dementia research in 2019, 41 were in the USA, six in the United Kingdom, and three in Canada (1). This inequity also hampers capacity building; even when LMIC researchers are involved as collaborators, a long-standing power imbalance remains with issues around fair representation, transparency and data ownership, and lack of strategies for sustainable funding and support to local populations after trials. Only 14% of countries frequently involve people with lived experience in aspects of research (1), despite them having the greatest interest in the outcomes and much to contribute.

To address these challenges, the World Health Organization (WHO) has developed *a blueprint for dementia research* (3) together with experts from around the world. The blueprint is inspired by previous efforts to coordinate research in the area of infectious diseases but is remarkably the first of its kind in the context of noncommunicable diseases. It aims to support the global prioritisation of dementia research and provides a coordination mechanism and a roadmap to facilitate timely and high-quality evidence, fast-track innovation and ensure successful implementation, as well as guide actions for mobilizing adequate resources for dementia research.

The blueprint summarizes the current state of dementia research across six broad research themes, identifies existing gaps, and outlines strategic goals with actions and timebound milestones to address those gaps. The six research themes consider the entire dementia research spectrum: 1) dementia epidemiology and economics; 2) dementia disease mechanisms and models; 3) dementia diagnosis; 4) drug development and clinical trials for dementia; 5) dementia care and support; and 6) dementia risk reduction. Throughout, the blueprint incorporates emerging scientific and technological advances such as artificial intelligence, multiomics, brain health across the life course and biomarkers to increase our understanding of underlying disease mechanisms and to foster early diagnosis and treatment.

Addressing these complex issues and existing gaps requires an enabling research environment. The blueprint therefore outlines eight drivers of research that are essential for accelerating dementia research. The drivers encompass: 1) the empowerment and engagement of people with lived experience in all areas of research; 2) promoting diversity and equity in dementia research; 3) appropriate and sustainable funding is allocated; 4) data-sharing to ensure better use of data, avoid redundancy, and promote a more inclusive research environment; 5) capacity building for research, especially in LMICs; 6) use of technology to drive innovation in the field; 7) knowledge translation and exchange to facilitate collaborations; and 8) strong and harmonised regulatory environments to support collaborations and research implementation. It is imperative to implement and monitor these drivers so that they become the norm rather than rare examples of good practice.

During the COVID-19 pandemic, we have learned how fast we can advance research and development if we act in a coordinated manner. The pandemic has also underscored the inequitable access to biomedical advances around the world and the urgent need to shift our approach to research towards global public health interest. Stakeholders at all levels — including people with lived experience, researchers, funders, and policy makers — must collaborate and set out comprehensive strategies for the adequate and timely response to dementia and ensure that research is more efficient, equitable, and impactful. As such, WHO encourages national and international research agencies, together with other funding bodies, to use this *blueprint for dementia research* to inform upcoming funding streams to guide their decisions and operationalize the outlined drivers of research. Civil society must ensure that advocacy efforts are likewise aligned, and researchers can support the achievement of milestones and strategic goals of this blueprint by addressing the research gaps identified.

The blueprint for dementia research represents a first step in establishing a global dialogue among stakeholders and provide guidance on future research activities for dementia. It is time to reach beyond our traditional ways of doing research and find better strategies to coordinate between sectors and stakeholders, including governments, multilateral organizations, academic institutions, civil society, people with lived experience and the private sector. If we want to halt the debilitating impact that dementia has on people and health and social care systems globally, we must come together and address these challenges collectively.

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Dr **Soumya Swaminathan** was appointed WHO's first Chief Scientist in March 2019. A paediatrician from India and a globally recognized researcher on tuberculosis and HIV, she brings with her 30 years of experience in clinical care and research and has worked throughout her career to translate research into impactful programmes.

Dr Swaminathan was Secretary to the Government of India for Health Research and Director General of the Indian Council of Medical Research from 2015 to 2017. In that position, she focused on bringing science and evidence into health policy making, building research capacity in Indian medical schools and forging south-south partnerships in health sciences. From 2009 to 2011, she also served as Coordinator of the UNICEF/ UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases in Geneva.

She received her academic training in India, the United Kingdom, and the United States of America, and has published more than 350 peer-reviewed publications and book chapters. She is an elected Foreign Fellow of the US National Academy of Medicine and a Fellow of all three science academies in India.

The Science division's role is to ensure that WHO stays ahead of the curve and leverages advances in science and technology for public health and clinical care, as well as ensuring that the norms, standards and guidelines produced by WHO are scientifically excellent, relevant and timely. Her vision is to ensure that WHO is at the cutting edge of science and is able to translate new knowledge into meaningful impact on population health worldwide.

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