

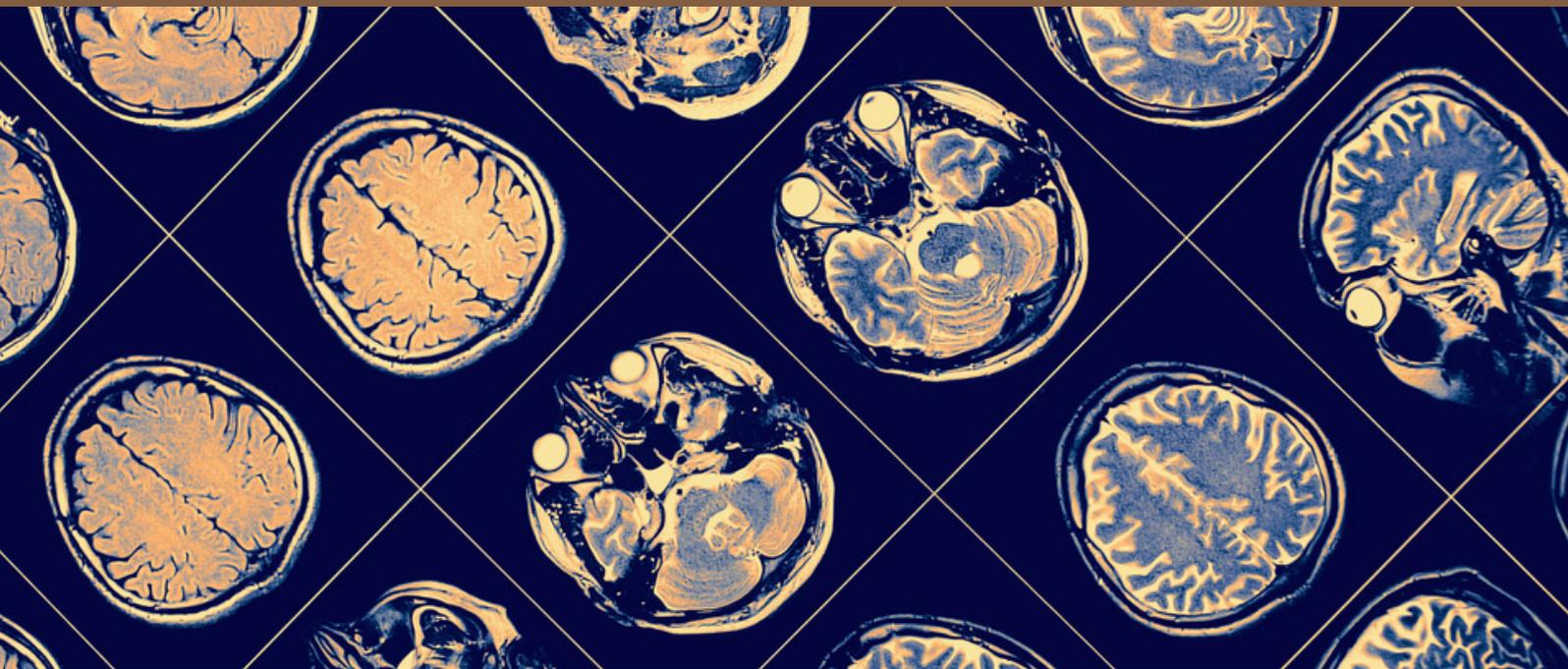


**World Dementia
Council** Leading the Global Action
Against Dementia

Research workshop: Reflections

The dementia landscape
project

Essays from international leaders in dementia



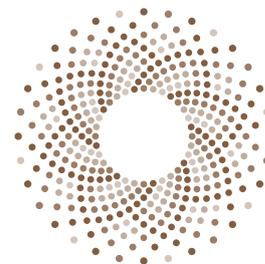
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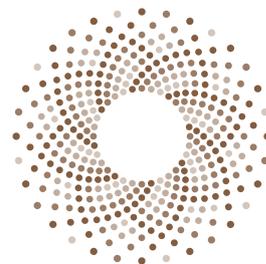
alzheimer's 
association

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1. Introductions



A relentless optimism taking us closer to our goal



Dr Maria Carrillo

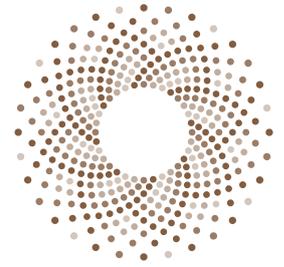
Chief scientific officer, Alzheimer's Association

Alzheimer's is relentless and so are we. The Alzheimer's Association was founded in 1980 by a group of family caregivers and individuals who recognized the need for an organization that would unite caregivers, provide support to those facing Alzheimer's and advance research into the disease. Over the last forty years our mission has not changed; and we are much closer to our goal.

As we all know, there is currently no FDA approved intervention to cure, slow or prevent the onset of Alzheimer's. But as both the workshop and these essays highlighted, we have made significant strides towards developing new treatments.

This is because of the steady accumulation of knowledge and understanding of the disease and its progression. And as our knowledge has accumulated, Alzheimer's research has identified many diverse biological targets of Alzheimer's, beyond the hallmark presentations of β -amyloid plaques and tau tangles. Recent advancements in how understanding and measuring the emerging pathology of disease, thinking about the disease as a continuum, developing tools to actively monitor disease-related changes in a living person, and new strategies for identifying and enrolling participants in clinical trials as well as confirmation of drug target engagement, means the pace of accumulated knowledge is increasing. And this means that today we stand are on the cusp of a new paradigm.

There are two factors I would highlight that have been important in making advances in the field to get us to this point – and remain important in advancing research. They are firstly the funding and the effective use of that funding, and secondly, collaboration. As the largest nonprofit funder of Alzheimer's and dementia research in the world the Association provides direct funding to researchers, including supporting and expanding the AD drug development pipeline. Currently, the Association is investing over \$208 million in 590 active best-of-field projects in 31 countries. These studies are targeting a wide variety of known and potential new aspects of the disease, such as inflammation and other promising new targets for therapy.



The Association has advocated for increased federal funding that has been critical over the last decade. In a polarized Washington we have developed and grown bipartisan support for critical policy priorities. Over the last decade the funding for the National Institutes of Health (NIH) for Alzheimer's research has increased from \$450 million to \$2.8 billion annually. As of fiscal year 2020, Congress agreed a \$350 million year-on-year increase. As a result of these significant increases, scientists are able to work at a more rapid pace to advance basic disease knowledge, explore ways to reduce risk, uncover new biomarkers for early diagnosis and drug targeting, and develop potential treatments.

As in the United States, globally we have seen increases in Alzheimer's research funding. As a community we need to continually champion the critical importance of that funding. As a field, proportionate to impact and need it remains underfunded compared to other disease areas.

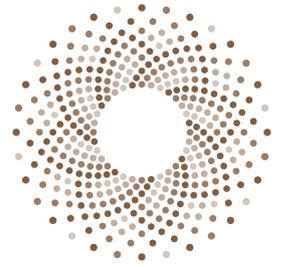
Nationally and internationally, we need to ensure that we have maximum impact for ever dollar we raise, or the taxpayer contributes. The Association has worked closely with the National Institute on Ageing (NIA) since our founding, collaborating in funding and recruiting participants for several flagship clinical trials. In 2011, workgroups jointly convened by the Association and the NIA issued new diagnostic guidelines for Alzheimer's disease and proposed a research agenda to define a new preclinical stage of the disease. In 2018, the Association and the NIA convened once again to publish a new Research Framework that proposes the use of biomarkers to detect Alzheimer's in its earliest stages.

One of the lessons I draw from the Covid-19 pandemic is the importance of scientific collaboration in accelerating progress. The sharing of knowledge, the building of relationships. The Alzheimer's Association International Conference (AAIC), the world's largest and most influential international meeting dedicated to advancing dementia science. The Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment (ISTAART) that brings together scientists, physicians and other dementia professionals active in researching and understanding the causes and treatments of Alzheimer's disease and other dementias.

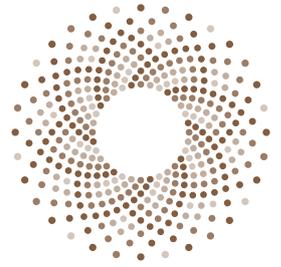
Alongside this we partner with key government, industry and academic stakeholders through a number of forums include ADNI, GAAIN, AMP-AD and GBSC to build collaboration. The Alzheimer's Association Research Roundtable, a consortium of scientists from the pharmaceutical, biotechnology, diagnostics, imaging and cognitive testing industries, and scientists from the NIH, FDA, European Medicines Agency, Health Canada and other government agencies, who seek to facilitate the development and implementation of new treatments.

Funding and collaboration are why we have been instrumental to making the progress we have and will be key in the years ahead. There are many challenges ahead. There is a significant gap in funding the identification and development of potential drugs before they are tested in humans. And there is a need for funding to bridge this gap, departing from traditional funding mechanisms by combining both expertise with the necessary know-how with the needed resources to translate more potential therapies to human studies. We must advance all potential treatment avenues and also explore methods

for combining these approaches. Alzheimer's and other dementias are complex, and their effective treatment and prevention will likely also be a complex – but achievable – task. All currently pursued treatments that are considered safe should be continued to determine their efficacy.



While there are many challenges to development of therapies for Alzheimer's and other dementia, the Alzheimer's Association has never been more optimistic than it is today.



A time for reflections

Professor Philip Scheltens

Professor of cognitive neurology and director,
Alzheimer Center, Amsterdam University Medical Centers
and member of the WDC



Optimism and Alzheimer's are not natural bedfellows. We as clinicians are often confronted with the frustration of being unable to offer our patients anything other than symptomatic drugs, care and support. The drum beat of trial failure accompanies us. And yet, despite this, now the field is at a turning point. It is the most exciting time in my thirty years working in the field.

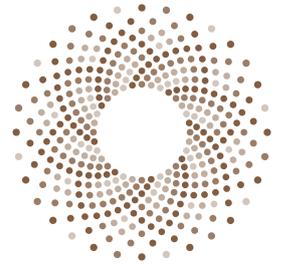
For so many people around the world, this has been a terrible year because of the Covid-19 pandemic. However, this year our field has seen exciting announcements in both treatments and biomarkers. But my case for optimism is not based on individual announcements, welcome that they are, rather on the fundamental building blocks that are now in place.

We know more about the basic science of the brain than ever before. The mechanisms that underlie Alzheimer's disease and other forms of dementia are much more complex than cardiovascular disease or oncology. We just know less about the biology of the brain than we do about the vascular system, but it is changing. There is a steady accumulation of knowledge which offers a wider range of potential targets for disease modifying treatments than ever before. And this will lead to new treatments.

We are on the trajectory that cancer has been on for many years, but 20 years behind. The first treatments will have some benefit to some people. But new generations of therapeutics will bring greater benefit. Whatever happens with Aducanumab's regulatory approval, within 5 years we will see disease modifying treatments.

Our understanding of the underlying biology of the disease means not just hope for therapeutics but also lifestyle interventions to prevent, or slow, the development of the disease. We have a much better understanding of genetics and the risk profile of developing dementia and patients who might benefit from interventions before the clinical manifestation of disease. As has been seen with cardiovascular disease and cancer, preventing the development of pathology is a viable and successful public health strategy.

Alongside these improvements in understanding of disease, in the near future we will be much better able to accurately diagnose it. Thanks to CSF and imaging we are already better able to stratify patients. Blood and digital biomarkers will soon have a huge



impact. We already understand more about the underlying genetic risk factors of disease, and genetic tests will become much more routine.

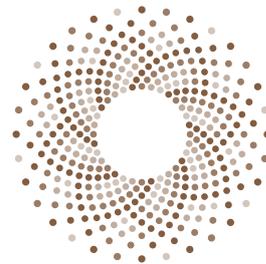
The benefits for clinical trials are obvious. With trials costing several hundred million dollars we are only going to have so many shots on goal. The potential to have trial ready cohorts that have biomarker profiles offers more flexibility in designing trials and the potential for delivering them both faster and cheaper.

Even without therapeutics, blood and digital biomarkers will benefit patients through the improved precision and timeliness of the diagnostic experience. Whether it prompts more patients to seek medical help earlier remains to be seen. The reason for patients presenting late are various, such as cultural factors or social and health system responsiveness. It may be that better diagnosis alone will not change behaviour.

Taken together, this means we should be confident that not only are we on the right trajectory, but that the pace of progress is increasing. Sustained funding increases along with well-developed funding strategies – from governments, not-for-profit organizations, philanthropy and the for-profit sector – have helped build capacity and knowledge in the field. Dementia remains relatively underfunded when compared to other disease areas. Maintaining and growing that funding, well developed and well executed funding strategies will be key. We will of course never have ‘enough’ funding. Over the last decade the sector showed how it can, with government and non-governmental partners, reduce financial risk through funding models. We need to continue to incentivize for-profit investment in the field. Utilizing big data offers plentiful opportunities to accelerate research but data sharing remains problematic. This is not a challenge we face alone as there are regulatory barriers right across scientific research, but other disease areas have done more to overcome it. Diagnosis, clinical trial recruitment and the cost of trials all, for different reasons, remain challenging.

But these are problems of pace and not direction. We are on the right trajectory. Over the last decade we have made huge progress. We can up the pace. This is a time to be optimistic.

2. Biomarkers and treatments



Blood-based biomarkers for Alzheimer's Disease



Professor Henrik Zetterberg
Professor of Neurochemistry, University of Gothenburg

Blood-based biomarkers have been described as the holy grail of biomarker AD research, because the promise of a simple, inexpensive, non-invasive test for AD is needed to accelerate observational and clinical trial research, diagnostics in the clinic and, when specific AD treatments are developed, allow appropriate identification of patients who would benefit. Recent AD blood biomarker discoveries have enabled both sensitive and specific measures of amyloid pathology, tau pathology and neurodegeneration.

Highly precise blood amyloid biomarkers were recently reported to have high concordance with both amyloid PET scans and CSF A β 42/A β 40 ratio,¹ the gold standard biomarkers for amyloid plaques. These recent developments were enabled by highly specific and precise measures of A β in plasma by mass spectrometry with the data from several hundred participants with high concordance of plasma A β 42/A β 40 with amyloid PET and CSF A β 42/A β 40. Independent work done in parallel also utilized mass spectrometry to measure A β 42/A β 40 and other fragments to demonstrate high concordance with amyloid PET and CSF A β 42.

With accuracies of greater than 80% and receiver operating characteristics (ROC) area under the curve (AUC) of >0.85, the precision of blood A β now matches that of CSF or PET with each other.² The robustness of the plasma test however, still remains a challenge; in CSF, the ratio is decreased by around 50% in amyloid-positive individuals, whilst the corresponding reduction is only 15% in plasma,³ which makes the test highly vulnerable to pre-analytical or analytical confounders.

Similar to CSF, phosphorylated tau species in plasma, such as P-tau181 and P-tau217, increase with disease progression in those with A β aggregates.⁴ These blood biomarkers seem to increase already at the onset of A β pathology and may represent a neuronal reaction to A β pathology, which precedes tau tangle pathology. There are now several immunoassays and mass spectrometry-based assays for phosphorylated tau species, showing high diagnostic accuracy for pre-dementia AD, available, and hopefully we will soon see automated high throughput clinical chemistry tests for this biomarker.

1. Ovod V, Ramsey KN, Mawuenyega KG, et al. Amyloid beta concentrations and stable isotope labeling kinetics of human plasma specific to central nervous system amyloidosis. *Alzheimers Dement* 2017; 13(8): 841-9; Nakamura A, Kaneko N, Villemagne VL, et al. High performance plasma amyloid- β biomarkers for Alzheimer's disease. *Nature* 2018

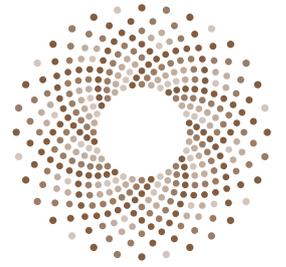
2. *Ibid*

3. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6946467>

4. PMID: 32333900; PMID: 33106600; PMID: 32123385; PMID: 32722745

5. PMID: 30967444

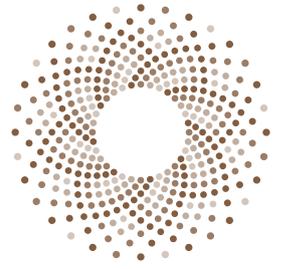
6. PMID: 30967444



Neurofilament light chain protein (NfL) is a well described blood biomarker in multiple neurologic diseases, including multiple sclerosis, stroke, traumatic brain injury, Parkinson's disease, PSP, and AD.⁵ Plasma NfL correlates well with CSF NfL and is a promising biomarker supporting AD progression correlating with cognitive and imaging decline.⁶ Recent studies suggest that plasma NfL increases around 10 years before symptom onset in autosomal dominant AD and predicts neurodegeneration and clinical progression.⁷ NfL is a promising blood biomarker to detect and quantify degeneration in AD but it is important to keep in mind that it is a general biomarker for any type of neuronal injury, which is important to keep in mind when interpreting its result.

The impact of very high accuracy blood tests for AD are enormous and promise to revolutionize clinical trial design, accelerating discoveries of novel interventions, enable historic cohorts to provide deep understanding of the start and progression of AD, and transform AD from an often misdiagnosed (and misunderstood) entity into an objectively diagnosed disease. For clinical trials, the ability to pre-screen thousands to hundreds of thousands of potential participants will improve the ability to decrease enrolment periods, shorten trial durations, and enable the launch and testing of more potential therapeutics. This will accelerate the discovery of new treatments. When we have access to disease-modifying treatments, the blood tests will enable primary care physicians to rapidly identify those patients who should be referred to a memory clinic to be evaluated regarding if they are available for active treatment.

7. PMID: 29070659; PMID: 30664784



Is the world ready for a new blood test for Alzheimer's disease?

Fiona Carragher

Director of Research and Influencing, Alzheimer's Society (UK)



Progress in world-leading research towards a new, accurate and early diagnostic blood test for Alzheimer's disease has moved at breakneck speed. To ensure that the benefits of this pioneering work are felt by everyone affected by dementia we must prepare the research and clinical community as well as the general public and all those affected by dementia. Are we ready?

Where are we today?

In the UK, the national target for dementia diagnosis rates is 66.7%.¹ In 2020 we saw a steady decline from 67.6%² in February to 64% in May³ leaving many thousands of people in limbo without a diagnosis. Alongside the impact of the pandemic, we know to date that the accuracy of a diagnosis is not guaranteed.

PET scanning techniques and CSF testing are available, recommended in the UK clinical guidelines and improve accuracy of a diagnosis but there is a huge variability in the accessibility, availability and uptake of these tests across the UK. The 2019 National Memory Service Audit reported that 56% of memory services have access to CSF examination and 77% to PET scans but the number of people referred to these services is very low.⁴

This may also be reflective of the fact many people are presenting too late when symptoms have progressed significantly, the substantial cost attached to these diagnostic techniques as well as capacity of current infrastructure.

What will it take to bring a new test to the clinic?

Great progress has been made in measuring biomarkers and changes in the brain during the presymptomatic phase of the condition. However, achieving the necessary validation of a new diagnostic test so that it may be adopted confidently across healthcare systems and into clinical practise is still a great challenge.

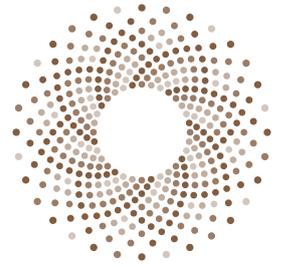
Focussed research that is prioritised and funded will be integral to continue refining these techniques and ensuring they are well validated and fit for purpose across a diverse population with complex clinical presentations.

1. Department of Health (2013). *Dementia: A state of the national report on dementia care and support in England*. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/262139/Dementia.pdf

2. NHS Digital (2020). *Recorded Dementia Diagnoses – February 2020*. Available at: <https://digital.nhs.uk/data-and-information/publications/statistical/recorded-dementiadiagnoses/february-2020> [Accessed 16 June 2020]

3. NHS Digital (2020). *Recorded Dementia Diagnoses – May 2020*. Available at: <https://digital.nhs.uk/data-and-information/publications/statistical/recorded-dementiadiagnoses/may-2020> [Accessed 16 June 2020]

4. The 2019 national memory service audit. Available at: <https://www.england.nhs.uk/london/wp-content/uploads/sites/8/2020/04/The-2019-national-memory-service-audit.pdf>



A key part of determining progress will be ensuring that any new suite of biomarkers is integrated into clinical pathways fit for the future; particularly if there is a move to earlier diagnosis. This may require changes in infrastructure such as integration of care across the traditional primary, neurology and psychiatry divisions, training of healthcare professionals in diagnostic interpretation and early debate and agreement on payment mechanism. This latter point cannot be underestimated and learning from challenges seen in the adoption of previous well-validated biomarkers in other clinical pathways, such as natriuretic peptide in heart failure, should be considered.

Going a step further

We have already seen the roll out of, though comparatively expensive, effective diagnostic techniques for Alzheimer's disease in the form of PET scans and CSF testing. However, we know uptake and access to these techniques varies hugely and they are often deemed unnecessary. Some reports suggest some clinicians lack confidence to make a diagnosis and do not always see the value of an early diagnosis.⁵

A blood test is likely to have greater uptake simply due to its cost-effectiveness, but this may not be sufficient motivation to improve uptake. We need to take a step further and ensure that attitudes across the clinical community that may be an additional barrier embrace and understand the true benefits of an accurate and early diagnosis.

Advocacy organisations such as Alzheimer's Society can play an integral role in raising awareness and understanding within the general public and those concerned about their risk of dementia of the value of an early and accurate diagnosis to the individual and altruistically.

Encouragingly, a report published in December 2019 by Alzheimer's Research UK and MSD demonstrated that, in a sample of over 2000 UK adults, 74% would want to know if they were going to develop Alzheimer's disease before symptoms are seen.⁶

It's clear that attitudes in the clinical community and general public will shift more readily in the event of a disease modifying treatment but improving accessibility of an accurate blood test itself could accelerate the likelihood of this becoming a reality.

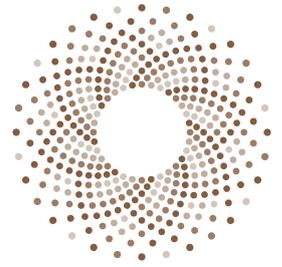
What would this mean?

The field of dementia is not alone in recognising a need for early diagnosis. We have seen huge progress in the field of cancer enabling personalised treatment and rapid diagnostics being critical in the Covid-19 response more broadly. There are great opportunities to learn from these fields.

An early and accurate diagnosis of dementia would provide great benefit to those living with the condition and their loved ones, empowering and allowing them to access emotional, practical, legal and financial advice as well as vital support services and available interventions. Additionally, an accurate diagnosis would reduce the number of tests and assessments required, minimise burden on health care systems, integrate care effectively and allow for better, more holistic care (and personalised treatment). Research has already indicated the use of biomarkers to validate a diagnosis influences

5. Ahmed, S (2010). GPs' attitudes, awareness, and practice regarding early diagnosis of dementia, *British Journal of General Practice* 60(578): 360-365.

6. Detecting and diagnosing Alzheimer's disease (December 2019). MSD, Dementia Access Taskforce & Alzheimer's Research UK. Available at: https://www.alzheimersresearchuk.org/wp-content/uploads/2019/12/1132267-Public-Perceptions-Report_v5.pdf



clinical management of patients.⁷ If we can ensure people are on the right care pathway earlier there is greater opportunity for equality in access and quality of care.

The test and the treatment

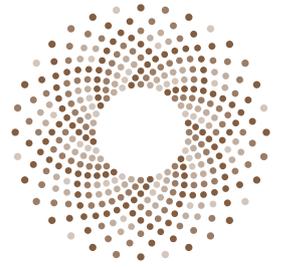
Alongside the benefits to the individual and healthcare systems, with 121 unique therapies for Alzheimer's disease registered on clinicaltrials.gov in May 2020,⁸ trialling new treatments in people at the very earliest stages of the condition with an accurate diagnosis will maximise the potential for success.

So, although a disease modifying treatment would be the ultimate driving force to embedding and ensuring the uptake of a blood test for Alzheimer's disease in clinical practise, this test itself could improve the chances of bringing new treatments to the clinic by allowing researchers to trial the right drugs on the right people at the right time.

We must not delay in taking steps to ensure healthcare systems are prepared to adopt and utilise an accurate, early blood test for Alzheimer's disease. It will not only provide benefits to the individual, but also drive development of disease modifying treatments and allow the right people to access them early, when they are available.

7. Rabinovic, GD et al (2019). Association of Amyloid Positron Emission Tomography With Subsequent Change in Clinical Management Among Medicare Beneficiaries With Mild Cognitive Impairment or Dementia. Available at: <https://jamanetwork.com/journals/jama/fullarticle/2729371>

8. Cummings, J et al (2020). Alzheimer's disease drug development pipeline: 2020. Available at: <https://alz-journals.onlinelibrary.wiley.com/doi/abs/10.1002/trc2.12050>



Reflections of blood based biomarkers for dementia: A brief response on opportunities and challenges



Dr Christopher Chen
Director, Memory Aging and Cognition Centre and
Associate Professor, National University of Singapore

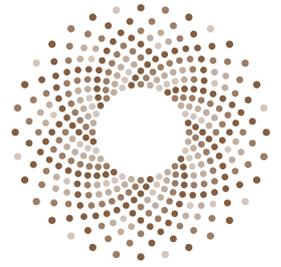
It has been nothing but astonishing to witness the recent emergence of blood based biomarkers for dementia. This has been built on not only advances in technology but also the laudable determination of researchers in this field to overcome disappointments and to persist. Moreover, much credit must also go to those who had the prescience to work on building the cohort studies which have been so well utilized to provide an evidence base. We are anticipating that blood biomarkers either singly or more likely in combination will dramatically change clinical practice as well as research.

Already a biomarker driven research framework has been proposed and provided much impetus for conceptual development and clinical trials. If validated, blood biomarkers will have an important impact on the diagnostic framework for dementia as biomarkers are added to or even replace current clinical diagnostic standards. Blood biomarkers potentially will improve access to and affordability of diagnosis and enable monitoring of disease modifying therapies. Blood biomarkers may also be particularly relevant in epidemiological research which has previously lacked such accessible disease markers, especially for early disease lacking in clinical symptoms. Such research may drive major public health initiatives for the prevention of dementia.

Validation will be facilitated by not only standardization, reduction in cost and increased availability of what have hitherto been research tools, but also by much more work on achieving more diversity in the data – studies have to be performed across different countries, ethnicities and case mixes. Dementia is not just Alzheimer pathology, there is a major contribution from cerebrovascular disease as well as from other neurodegenerative diseases, Primary Age Related Tauopathy, Lewy Body Disease, hippocampal sclerosis, TDP-43, agyrophilic grain disease to name a few.

Studies are needed to assess the effect on blood biomarkers of the multiple mixed pathologies common in most patients with dementia and how they may influence or be influenced by upstream and downstream biomarkers of pathophysiology and neurodegeneration.

Finally, confirmation by clinical trials of the use of blood biomarkers for diagnosis, prognosis, prediction of treatment effect and as surrogate end points will drive acceptance of blood biomarkers in the prevention and management of dementia.



Reasons for optimism: The state of Alzheimer's Disease research in 2020



Dr Husseini Manji

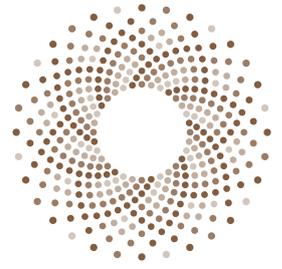
Global Head, Science for Minds, Johnson & Johnson

There is reason to be optimistic for the future of Alzheimer's disease (AD) research, despite the recent trial failures with compounds developed for AD disease modification. This optimism is firmly grounded in the potential of tau as an effective target, the growing diversity of drugs in clinical trials including those targeting the immune system, and the continued development and use of biomarkers.

If we are to hit the ambitious goal of having a disease modifying therapy (DMT) by 2030, a great deal rests on whether tau will prove a better target than – in the broadest sense – amyloid. On this front, there is reason for optimism, namely the clear relationship between tau pathology and AD, and genetic evidence that tau is a driver of neurodegeneration and, therefore, an effective target for therapeutic developments. This optimism is supported by the previous decades of research leading to the breakthrough in understanding that the characteristic spread of pathology may be a consequence of the interneuron seeding of pathological tau. This breakthrough has led to the development of tau-directed immunotherapies, and it is with these molecules that the greatest hope for a DMT by 2030 resides.

As a result of the inherent challenges in treating AD, potentially the most essential development is the continued growth in diversity of targets within the landscape of drug development. A strong diversity of targets is necessitated by the complexities of the brain and difficulty accessing it, along with the need to understand the disease's biology in order to create effective targeted interventions. The recent setbacks with drugs targeting amyloid plaque further underscores this need. The ability of genetics to provide answers to questions regarding the immune systems role in AD, such as whether immune dysfunction is a driver of the disease or simply a response and which of the multitude of targets is likely to prove most effective, has led to an increase in the number of immune targets in development. Questions remain, namely which pathway of immunity to target and given the significant possibility that the immune system could have both protective and deleterious effects at different stages of the disease, when to target it. Yet, the rapid increase of immune targets in development, including compounds that modulate neuroimmune regulation, is a very positive sign.

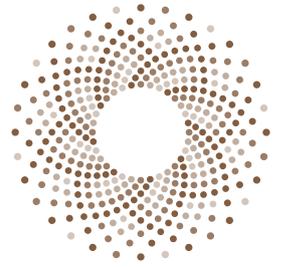
If the field is to see eventual success in the development of an effective DMT, biomarkers are likely to continue to play an essential role in the improvement of clinical trials. The combination of increasingly sophisticated biomarkers and the continued recognition of the heterogeneity of pathological process in people with AD is enabling trials in which



participants are defined on entry by pathological measures. Additionally, one of the challenges of having cognition as the primary outcome measure for disease modification trials is the inherent daily fluctuations that occur in individuals' cognitions. Biomarkers have the opportunity to reduce some of that variability leading to more rapid decision making for futility or acceleration in phase two trials, along with proof-of-concept studies.

The coming decade will invariably bring failures with it, requiring companies and governments alike to stay steadfast in their commitment to creating an effective treatment for this difficult and growing disease. Yet, that commitment is already evident in the continued research and increasing diversity of targets. The potentially significant developments within tau pathology and in biomarkers allows for improvements in clinical trials when it comes to screening, selection and increasingly proof of concept. It is essential that we remain optimistic and learn from our past mistakes as we continue to work towards developing an effective treatment for AD.

The author would like to acknowledge Sir Simon Lovestone, vice president and disease area stronghold lead for neurodegeneration, Janssen, for the ongoing discussions that have influenced the thinking and work presented in this essay.



The preclinical Alzheimer's disease research infrastructure challenge: Looking ahead



Dr Ivan Koychev

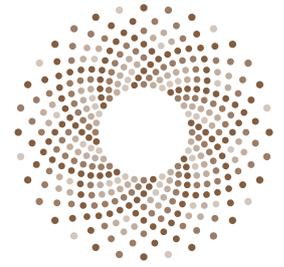
Clinical academic psychiatrist, University of Oxford

'One more question, Doc' is now a regular parting shot from the son or daughter of a patient I have just diagnosed. It is dropped in just as they are about to leave, almost an afterthought. Typically we have spent the last hour painting the picture of the road ahead for the family; the trauma of shifting from the role of a grown-up child to one of a carer, a succession of losses, and ultimately the fading of the person once known. And yet, while in past, the stunned family may have silently filed out deep in thought, we are now standing by the door opening a new conversation.

'What can I do not to get this?' It is difficult to overstate the opportunity for dementia research that is contained within this repeated question. The concept of the 'right treatment to the right patient at the right stage' put forward by Reisa Sperling and colleagues a decade ago is so widely accepted that stating it in research context is by now almost trite. However, for pre-clinical disease, the pursuit of treatments faces the specific challenges of conducting clinical studies in asymptomatic populations. Availability of suitable biomarkers apart, perhaps the fundamental challenge is the scarcity of research infrastructure to detect, track and investigate disease progression from its earliest stages. Even health care systems that are highly centralised, such as the UK National Health Service are simply not geared-up to detect, let alone treat pre-symptomatic dementia.

Research registers or trial-ready cohorts such as the Great Minds registry that we at Dementias Platform UK have developed or the recently concluded European Prevention of Alzheimer's Dementia study address this gap. They use genetics and longitudinal (lead-in) data for precision risk-stratification and enrolment to mechanism-specific studies. However, the problem is they are relatively homogeneous and an order of magnitude too small. Whilst they are an excellent resource for experimental medicine and early phase trials, they would be a rapidly depletable and non-diverse resource for efficacy studies. We need to think bigger and broader.

Enter the adult children of my patients; individuals in their late mid-life years who are used to being active players in the management of their physical health through seeking relevant research information and maintaining a healthy life style. Typically they are well-versed in the use of digital technologies to track their risk factors. It is only natural that they wonder why, if they are able to look after their physical health, should that not be possible for their brain health? And if it is possible for brain health, would they not be the ideal partners in our challenge to demonstrate efficacy in pre-clinical disease? I believe that four key developments over the past decade make this now a realistic option:



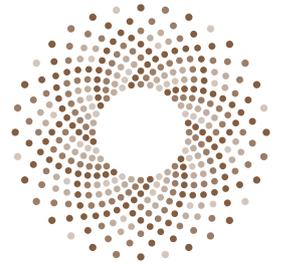
1. Improved understanding of risk factors. The gradual accumulation of evidence from a number of high-quality epidemiological studies have given us a firm understanding of the modifiable and non-modifiable risk factors of dementia. Combining these risk factors in predictive models is shown to be highly informative in identifying those at high risk of being along the AD spectrum giving us the ability to detect the ‘right patient’. In a recent analysis of the NIH-funded Baltimore Longitudinal Study of Aging and BIOCARD cohorts we also been able to demonstrate a critical time-point during the life course marks a rapid escalation in the rate of AD biomarker accumulation providing us with the ability to define the ‘right stage’. Combining this knowledge provides an, until now, unavailable opportunity to give ageing individuals the ‘If’ and ‘When’ of their personal dementia risk.

2. Rapid development of digital technologies. We have seen a rapid expansion of digital technologies that are capable of characterising cognitive health longitudinally. The low hanging fruit has naturally been the porting of cognitive testing to smartphones and other personal digital devices. Tracking of the passive use of these digital devices provide a further opportunity to characterise cognition longitudinally, which when combined with the active testing massively expands the potential to detect deviations in an individual’s cognitive baseline. This has the dual benefits of both identifying those on the cusp of being symptomatic and also of reducing the clinical trial sample sizes by using long-term cognitive trajectories to uncover beneficial effects of novel treatments which may otherwise have been lost to noise. Further developments go beyond simply tracking cognition and in fact put the user in control of their AD risk factors with coaching support to achieve preventable risk factor modification; its utility already demonstrated by the FINGERS suite of studies. The advances of these digital technologies when combined with the deep penetration of the required devices across societal strata provide a major opportunity to track cognition and empower proactive brain health management. Crucially, this introduces diversity to research, democratising access to the latest dementia research beyond the unrepresentative group of typical research volunteers.

3. The blood biomarkers boom. The third component is the remarkable development of highly specific, non-invasive means for evidencing AD pathology through plasma testing as highlighted by Henrik Zetterberg in his essay published here. They provide the opportunity to detect dementia, distinguish subtypes, and track progression at the scale required to deliver highly informative clinical trials at feasible costs.

4. Data linkage and sharing. The last component is the recognition of the importance of data linkage and rapid data access to researchers to accelerate research through projects such as Dementias Platform UK Data Portal and the recently announced Alzheimer’s Disease Data Initiative Workbench. These platforms enable multi-modal research and clinical data to be integrated at-scale.

All of these advances provide us with a unique opportunity to establish the research infrastructure fit for the challenge of tackling preclinical dementia. And so we come back to the critical component in all this – the force behind the question of my patients’ sons and daughters. This is the time for them to make their mark on dementia research, and it is our duty to help them achieve it.



The research, development and dissemination (RDD) ecosystem required to achieve the 2025 goal of new therapies for Alzheimer's Disease



Professor Jeffrey Cummings

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The European Union Group of Eight (G8), meeting in 2013, set the ambitious goals of identifying a cure or a disease-modifying therapy (DMT) for dementia by 2025 and increasing collectively and significantly the amount of funding for dementia research to reach that goal. The development of DMTs as well as new therapies to improve cognitive function and reduce neuropsychiatric symptoms of Alzheimer Disease and Related Disorders (ADRD) requires development, funding, maintenance, and continuous refinement of a complex research, development, and dissemination (RDD) ecosystem. Some of the RDD elements are currently in place, some are not, and the pieces are not integrated into a system that seamlessly advances discoveries, innovations, and treatments through a system designed to deliver drugs equitably to the world's population.

Figure 1 shows the major elements of the RDD ecosystem required to advance therapeutics to reach individuals with or at risk for ADRD. Foundational Science is critical to advance therapeutics and is the origin of the research and innovations that will move through the ecosystem. Basic research in ADRD is currently underfunded. This is reflected in the relatively small number of agents in Phase 1 clinical trials. Most Phase 2 and Phase 3 drugs (excluding repurposed or repositioned treatments) are derived from Phase 1; the lack of a robust cohort of Phase 1 agents impedes progress in developing urgently needed therapies. The Foundational Science required for the RDD ecosystem includes target identification, screening and optimization of candidate therapies, and assessment in nonclinical models for both efficacy and safety. Model test systems that better predict human efficacy are needed to optimize progress through the ecosystem.

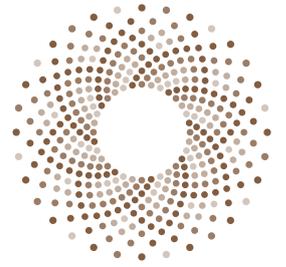
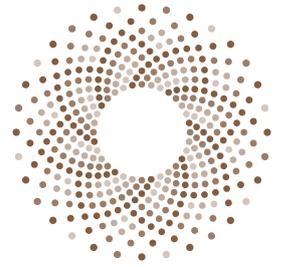


Figure 1: Research, Development, and Dissemination (RDD) ecosystem required to advance new therapies that will reach individuals with or at risk for Alzheimer’s disease globally.

Translational Science links the foundational observations to the drug development and clinical trial process. Biomarkers, definition of ADRD populations, and application of pharmaceutical medicine are the major elements of this aspect of the RDD ecosystem. There has been marked progress in ADRD Translational Science. Brain imaging is now available for amyloid beta protein (A β) aggregated in plaques, neurofibrillary tangles, microglial activity, synaptic proteins, brain metabolism, and several important transmitter receptors. An explosion of magnetic resonance imaging (MRI) techniques allows study of brain volume (total and regional), cortical thickness, white matter integrity, resting and activated functional networks, and molecular content identifiable with spectroscopy. Cerebrospinal fluid (CSF) measures have been developed for the A β (A), tau (T), and neurodegeneration (N) elements that comprise the ATN Framework for AD including measures of the A β 42/40 ratio, p-tau, total tau, neurofilament light (NfL), and neurogranin. There has been remarkable progress in blood-based biomarkers that will be game-changers in ADRD diagnosis, differential diagnosis, clinical monitoring, and clinical trials. Measures of all ATN components are now accessible peripherally in blood. The ATN Framework can be expanded to ATNx to allow inclusion of markers of inflammation, vascular disease, bioenergetics, and other factors reflecting the expanding understanding of the neurobiology of ADRD. Advances in biomarkers have



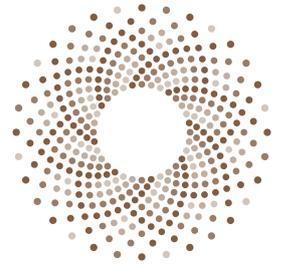
facilitated the identification of ADRD prior to disease onset. AD is recognized to have a long (15-20 years) asymptomatic preclinical phase followed by a mildly symptomatic prodromal phase prior to progressing to mild, moderate, and severe AD dementia. An expanding toolbox of biomarkers is emerging that will facilitate trials and interventions across the AD continuum. There is currently a lack of linkage between the clinical phenotype and available biomarkers that may be resolved with better clinical measures, a wider range of biomarkers, and markers of brain resilience. Pharmaceutical Science is central to successful drug development and the RDD ecosystem and addresses key pharmacologic properties of the candidate therapy including human pharmacokinetics, pharmacodynamics, pharmacogenetics, dosing and dose-response relationships, blood brain barrier penetration, and drug safety.

Translational and Foundational Science come together in the human experiment of clinical trials. Trials are complex enterprises that involve patient recruitment, dedicated sites with trained personnel, institutional review boards, research pharmacies, clinical testing, biomarker collection, and transfer of critical data to the trial sponsor. There are few standing trial organizations, and for most trials the trial network must be built anew by the sponsor and contract research organization for each trial. This is highly inefficient. Organizations such as the Global Alzheimer Platform (GAP), the US Alzheimer Clinical Trial Consortium (ACTC), and the European Prevention of Alzheimer Disease (EPAD) network are examples of standing organizations aimed at improving site efficiency, enhancing participant recruitment, using central review boards, implementing master agreements with industry sponsors, and developing new sites to expand the network. A more efficient approach is the platform trial organization ---- pioneered in AD by EPAD and the Dominantly Inherited Alzheimer Network – Treatment Unit (DIAN-TU) --- that allows simultaneous assessment of multiple agents, use of a shared placebo group, comparison of clinical and biomarker outcomes across multiple types of interventions, and use of more flexible adaptive clinical trial designs.

There are too few trial platforms and greater trial capacity of this type is urgently needed. Recruitment is a major challenge with the time required for recruitment exceeding the treatment period in most trials. Clinical trials currently lack diversity; most participants are highly educated Caucasians. Diversity, equity, and inclusiveness must be built into trials in anticipation of the needs of diverse users when a successful agent is disseminated.

Data volumes and diversity are growing at a daunting pace. Data Science and Informatic strategies at the operational level (e.g, interoperability, integration of scale) and analytic level (e.g, artificial intelligence, machine learning, deep learning) are needed. Data from the level of laboratory screening of drug candidates with assays to the recruitment of patients should reside in accessible repositories allowing novel interrogation. Every trial and experiment are learning experiences that can inform the next trial or experiment. Forward translation informs use of clinical trial agents in clinical practice and reverse translation informs drug development at the nonclinical level. Curated data inform regulatory decisions. The limited availability of data scientists is a challenge to advancing the RDD ecosystem.

Regulatory decision-making may seem fixed and inflexible, but Regulatory Science advances like all types of intellectual and scientific pursuits. Progress in understanding



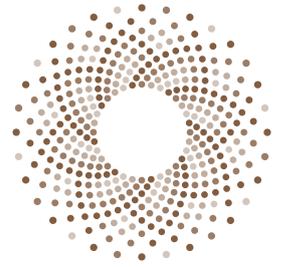
ADRD requires simultaneous advances in Regulatory Science to judge the quality of information collected on new populations, role of new clinical outcomes, validity of emerging biomarkers, or implications of novel analytic strategies. Regulators must judge the efficacy and safety of candidate treatments, and Regulatory Science must evolve in concert with Foundational Science, Translational Science, and clinical trial execution to adequately assess the information generated. There are too few individuals trained in Regulatory Science and too few training opportunities for those who will comprise the regulatory workforce of the future.

Dissemination Science is the critical link between drug discovery and development and impacting public health. The Covid-19 experience has provided many valuable lessons; among these is that there is a wide gap between having a therapy such as vaccine and getting it to those who need the therapy (i.e, vaccination). This same challenge will be faced with successful treatments for ADRD. If the therapies are complex such as monoclonal antibodies, substantial health care system infrastructure will be required including expert diagnosticians, amyloid imaging capability, infusion centers for treatment administration, and MRI availability to detect side effects. Health care systems are currently unprepared to deliver effective new therapies. Especially DMTs. Many persons with preclinical and prodromal disease are unaware of their jeopardy and educational campaigns will be key to treatment dissemination. Science of Behavioral Change (SoBC) learnings are needed to know how best to engage diverse communities and achieve global equity in treatment.

The result of an integrated RDD ecosystem will be improvement in public health at the societal level and relief of patient and caregiver suffering at the individual level. This will happen only with the involvement of many types of funders, supporters and stakeholders. Governmental funding (federal, state/province), support from patient advocacy groups, contributions from philanthropists, investment from venture capital funds, and support from the biopharmaceutical industry and others are all required to support the RDD ecosystem. Public-private partnerships have proven to be a successful means of distributing costs and sharing risk and should be championed with companies and governmental agencies. More funding is necessary to address the scale of the challenge involved in developing and disseminating treatment; sustained commitments are essential given the multifaceted issues of ADRD. Coordination of funding would help ensure that all elements of the RDD ecosystem receive support and are available when needed.

Phase 3 for a DMT requires approximately 5 years to execute including 2.5 years of initiation and recruitment, 18 months of treatment, and 1 year for data analysis, dossier creation, and regulatory review. This time calculation demonstrates that for a treatment to be approved by 2025 as planned by the G8, the agent must currently be in Phase 3. No Phase 2, Phase 1 or laboratory compound can be advanced sufficiently rapidly to meet the 2025 deadline. A few agents are poised for trial completion and possible approval given positive outcomes by 2025. We cannot in this period produce a repertoire of therapies that will meet the diverse needs of ADRD patients for treatments to prevent or delay progression, improve cognition, or reduce the neuropsychiatric symptoms that accompany these complex disorders. We can advance some treatments, and more importantly, we can understand the RDD ecosystem and build the integrated, learning, inclusive enterprise required for on-going and future successful treatment development.

3. Conclusions



Dementia – reflections during a pandemic



Professor Bart De Strooper

Director, UK Dementia Research Institute, Professor and VIB researcher, KULeuven, Belgium and UCL, London

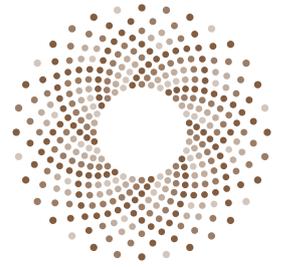
No group have been harder hit by Covid-19 than people with dementia. A tragic increase in deaths has been accompanied by a devastating increase in isolation, and the pandemic has only served to highlight the magnitude of the challenge posed by dementia. In time, thanks to concerted efforts, the pandemic will pass. Without the same force of will, the growing dementia crisis, with huge societal and financial costs, will remain.

Why then, despite the desperate medical need and the powerful economic arguments, are there no disease-modifying treatments for dementia? The answer is multifaceted and certainly in part to do with the complexity of the human central nervous system and the inherent challenges in conducting research on the brain. However, it is worth looking at two additional points.

First, there is a major knowledge gap in our basic understanding of Alzheimer's and other neurodegenerative diseases. The number of published research articles on cancer is a staggering 15 times greater than those published on Alzheimer's disease. Clearly, we have only just begun to unravel the complex pathology of dementia – a complexity that will ultimately have to be reflected in the design of new treatments, which are likely to consist of a multi-modal or combination therapy rather than a single 'silver bullet'.

The second point is also one of scale. Consider – since the year 2000, about 2,400 clinical trials (all phases) were undertaken for Alzheimer's disease. In the same period, around 74,000 trials were undertaken for cancer. And while some may assume that the clinical trial success rate for cancer is much higher, this is not actually the case: the proportion of phase 3 trials since 2000 resulting in FDA-approved drugs for cancer is around 3% (238 out of 7359 trials), whilst for Alzheimer's disease it is 2% (5 out of 252 trials).

The cancer field has clearly shown that innovative, effective therapeutic approaches and improved health outcomes are only achievable with sustained commitment to research. If we are to substantially reduce the number of people developing dementia, comparable



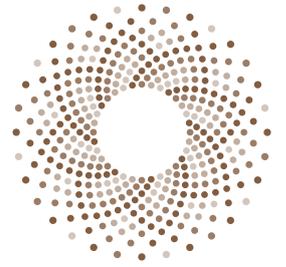
investment in research, researchers and supporting infrastructure needs to be made. And yet, despite the tremendous unmet medical need, the dementia research field remains woefully underfunded. Of particular concern is the lack of a focus on dementia in Horizon Europe, the European Union's new flagship research framework programme. Early drafts of the work programme mention the words 'brain' and 'neurodegenerative diseases' only once or twice, and Alzheimer's disease not at all.

While the UK is doing better, with Government committing to double annual spend on dementia research, a bigger effort is still needed. For instance, there are approximately 26,000 researchers working on cancer in the UK, but just 6,000 on dementia, despite the fact that as many people die with dementia as cancer. Investment is urgently needed to build research capacity to deliver on Government ambitions to find life-changing treatments. And public funding will be crucial to bridge the divide between investment in academic research and in industrial research and development. We must continue to invest in research excellence to better understand the range of complex disorders which result in dementia and drive new approaches to diagnosis, treatment, care and prevention.

This is not to say there should be a focus on dementia at the expense of cancer. Rather, success in cancer research shows what is possible. Fortunately, there is an increasingly solid foundation on which to build. New technologies that were simply unimaginable just a few years ago are now offering opportunities to understand the brain across the entire spectrum – from sub-cellular and single-cell resolution through to real time neural network dynamics. Recent discoveries in human genetics and biology of disease have yielded important insights that have pushed research in new directions. These, together with progress in imaging and early diagnosis, will lead to earlier recognition of risk and illness itself, meaning people will be healthier and younger when diagnosed. This in turn will mean we can intervene in the early stages of disease before major damage to the brain has occurred.

Novel therapeutic approaches are on the horizon too, such as oligonucleotides, cell and gene therapies that make early, targeted interventions possible. New ways to enable therapeutics to cross the blood brain barrier provide perspectives on the use of antibodies and other biologicals to treat human brain disease. These promising developments demand an intensification of our mechanistic discovery science. Investigating the prodromal phases of neurodegeneration, addressing questions such as selective vulnerability, resilience, plasticity and repair, initial inflammatory responses and homeostasis across different dementia-causing diseases, requires a multidisciplinary effort. At the same time, it is crucial to bring basic and clinical researchers even closer – to validate discoveries in systems relevant to human biology and allow clinical observations to inform new hypotheses to test in the lab. This work will fill the translation pipeline with fresh and innovative concepts for therapeutic development.

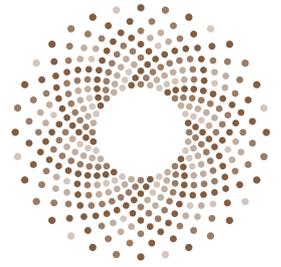
2020 will remain in history as the year of the Covid-19 pandemic. It has posed huge challenges for people with dementia, with loss of routine and social contacts under lockdown hastening cognitive decline in many. We now know that people with dementia are highly susceptible to the virus – in the UK it has been the most common pre-existing condition in those dying from Covid-19. And, with extreme pressures on the health and care system, deaths from dementia have tragically also risen. It is worth



noting that between January and November 2020, Covid-19 was the second most common cause of death in England – behind dementia and Alzheimer’s disease.

There are fundamental lessons to learn from the Covid-19 pandemic for us all. This crisis has taught us how coordinated research efforts can rapidly attract, focus and deliver effective solutions to major global health challenges. These rely on a critical mass of dedicated researchers and clinicians advancing scientific knowledge and driving solutions in collaboration with industry partners and regulatory agencies, with streamlined procedures for clinical trials, data sharing and substantial government investment. We must tackle dementia with the same spirit and sense of urgency.

Now, more than ever, is the time to invest in dementia research and support the next generation of talented researchers. With several vaccines on the horizon, Covid-19 will eventually be defeated – dementia will remain our biggest health challenge.



The importance of dementia research



Ernst van Koesveld

Vice Minister, Long-Term Care, Ministry of Health, Welfare and Sport, The Netherlands

Investing in dementia research should be a top priority. For both funders and scientists. Worldwide.

We all know the salient figures on dementia:

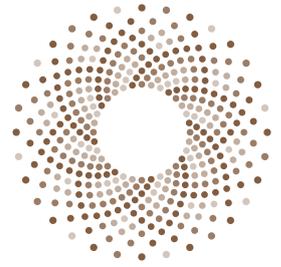
- There are currently estimated to be over 50 million people worldwide living with dementia.¹ The number of people affected is set to rise to 152 million by 2050.
- Every 3 seconds, a new case of dementia arises somewhere in the world.
- The worldwide costs of dementia are now above US\$1 trillion.

People with dementia are faced with an increasing loss of cognitive skills. This has a great impact not only on the life of the person with dementia but also on their loved ones. A person with dementia increasingly needs support and guidance, even though he or she may still be physically able to do much. In a more advanced stage of dementia 24/7 supervision is needed. Due to the cognitive decline, the “person everyone loved and knew” gradually disappears. This leads to a process of mourning that can last for years before the actual death of the patient. The combination of these factors makes living with someone with dementia especially difficult. Especially for the partner, who is also often quite old. If dementia develops at a relatively younger age (< 65 years), additional issues, such as the presence of (young) children still living at home and the loss of income, also come into play.

That is why we need to invest in dementia research. Research to improve treatment, care and support for people with dementia and their families. But foremost, research to find ways to prevent and cure dementia. With the ultimate goal: a world without dementia. For the past years scientists have accumulated knowledge about the biology of the brain. Although this has not yet translated into therapeutics, it does mean they have a range of potential targets for disease modifying treatments. And this will lead to new treatments. This knowledge may also lead to lifestyle interventions to prevent or slow the development of dementias.

The Dutch government supports initiatives like the World Dementia Council in order to improve the quality of life for those living with dementia and to initiate and support research into prevention and cure. In October 2019, Deputy Prime Minister and Minister of Health, Welfare and Sport, Mr Hugo de Jonge, called upon the G20-countries to double their investments in dementia research. This call was to be followed by a Ministerial

1. Alzheimer Disease International



Summit aiming at, among other goals, a joint effort to boost dementia research worldwide. Due to the Covid-19 pandemic this summit had to be postponed. However, this did not prevent the Dutch government from presenting its National Dementia Strategy 2021-2030² on World Alzheimer's Day 2020.

This dementia strategy has three main themes:

“Persons with dementia matter”

Our aim is to ensure that persons with dementia are given the opportunity to continue playing a role in society in line with their wishes and capabilities. This means, on the one hand, making an effort to provide persons with dementia with opportunities to engage in fulfilling activities, such as doing volunteer work at sports clubs or community centres. On the other hand, it also means contributing to a structural change in behaviour on the part of other people so that people with dementia can continue to feel that they are a part of society. We continue the programme on dementia friendly society, with special attention to the involvement of young people.

“Tailor-made support when living with dementia”

In recent years, the “Dementia Care for Each Other” programme has taken steps in further improving the support and care provided to persons with dementia and their loved ones. In the coming years, we aim to continue this process, for example by strengthening the regional dementia care networks. This includes the neighbourhood care teams, implementation of the dementia care standard, and - at the national level - focusing on collecting, broadening, and maintaining and spreading knowledge about all aspects of support and care for persons with dementia and their loved ones.

“A world without dementia”

Since 2013, the national research programme “Memorabel” has focused on researching all aspects of dementia. In 2021, The Netherlands will start a ten-year research programme, with the ultimate goal to be able to cure and prevent dementia. Research in the top sector Life Sciences & Health is aimed at improving the quality of life of persons with dementia. Collaboration and coordination with other research initiatives, nationally as well as internationally, are crucial for achieving the ultimate goal. To enable this ambitious research programme, the government contribution to dementia research is doubled and now amounts €148 million over a ten-year period.

With this national dementia strategy we aim to make a difference for those living with dementia. We hope it also encourages other countries to set up national dementia plans.

The recent WDC workshop on research showed optimism. Researchers shared their believe that they will find ways to prevent and cure dementia. As governments, we have to support researchers to make this believe become a reality. Let me repeat our call in Japan in October 2019: join hands and increase the investment in dementia!

2. National Dementia Strategy 2021-2030, Government.nl
<https://www.government.nl/documents/publications/2020/11/30/national-dementia-strategy-2021-2030>

The World Dementia Council (WDC) is an international charity. It consists of senior experts and leaders drawn from research, academia, industry, governments and NGOs in both high-income and low- and middle-income countries, including two leaders with a personal dementia diagnosis. The WDC has an executive team based in London, UK.

worlddementiacouncil.org

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