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# Emerging Trends in Biomedicine and Health Technology Innovation

ADDRESSING THE GLOBAL CHALLENGE OF  
ALZHEIMER'S

OECD

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## FOREWORD

Enabling innovation in biomedicine and health technology is a priority area for the Committee for Scientific and Technological Policy (CSTP) and its Working Party for Biotechnology (WPB). It builds on work on Alzheimer's disease that began at a small expert meeting in June 2011 hosted by the Business Industry Advisory Council (BIAC) and on discussions with experts.

The original draft of the report was prepared by Dr. Zaven Khachaturian (President of PAD2020 - The Campaign to Prevent Alzheimer's Disease by 2020) and the report was finalised in close co-operation with the OECD Secretariat.

The Committee for Scientific and Technological Policy (CSTP) agreed to the declassification of this report in April 2013.

The report is published under the responsibility of the Secretary-General of the OECD.

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## EXECUTIVE SUMMARY

The economic and social impact of chronic brain disorders (CBD) such as Alzheimer's disease (AD) and other neurodegenerative diseases will become the number one public-health problem worldwide, directly affecting 100 million people by 2050. On-going demographic trends, namely ageing populations worldwide, are leading to the unprecedented expansion of consumer demand for healthcare services. Healthcare systems worldwide will soon confront a serious crisis as a result of significant growth of the healthcare market, in a climate of shrinking resources. Such disorders impact not only the health sector but also prevent people from leading fulfilling and productive lives and making their full contribution to the economy and society.

Alzheimer's disease (AD) is one of a number of ageing-related chronic conditions that will place an enormous burden on healthcare systems because of the need for prolonged care and the resultant high consumption of resources. Thus, focusing on the management of AD as a proxy for the larger problem offers a test case for approaching the complex challenges that need to be addressed, including scientific and clinical research, technology development, care delivery, public policy, insurance and other financial issues, and psychosocial burdens to caregivers.

Following three decades of effort to understand the working of the brain and the reasons behind neurodegenerative diseases, the international scientific community is supportive of the efforts to strategically focus global actions to discover and develop more effective treatments to address the global challenge of AD. They believe that a broad spectrum of interventions to reduce the prevalence of disability – by delaying the onset of symptoms, or modifying the progression of the disease, or (eventually) preventing the disease – could be achieved through concerted collaborative effort within a decade. However, numerous scientific, administrative, regulatory, infrastructure and financial obstacles must be overcome within the next decade to make this vision a reality.

The report concludes by proposing a roadmap for action for OECD countries to consider. It lays out the critical issues to be considered in developing a multi-national plan to tackle the global challenge of this and other neurodegenerative disease, i.e.:

- Harmonising the development of international R&D resources and capabilities;
- Facilitating the process of technology transfer – knowledge mobilisation to discover-validate early markers of AD;
- Establishing a framework for 'Public-Private Partnerships' for collaborative R&D projects; and
- Creating new model(s) for the governance and financing of multinational collaborative research and development actions.

## INTRODUCTION

Human life span continues to increase, leading policy makers and economists to be concerned about the social implications of the future demand for health care. As a result of both better health in the general population, particularly in the more developed countries, and a decrease in fertility, it is anticipated that, by mid-century, roughly one-third of the global population will be in the category traditionally considered “elderly,” and the proportion will reach over 40% in many G-20 countries, putting unprecedented pressure on social and economic policies.

These demographic trends necessitate the careful management of the relationship between supply and demand, particularly in a time of fiscal crises. But healthy ageing is not an issue for the health sector alone. More broadly, governments must simultaneously manage spending on research, long-term care, preventive and therapeutic medicines and interventions, and social integration in an environment of older adults having greater economic power but often being marginalised. Ageing and ensuring that ageing is healthy, is a priority for reasons including economic productivity, financial stability and sustainability, social engagement, human rights and ethics. Biotechnology has its role to play in enabling people to live longer and healthier lives, lives which will be both productive and fulfilling at economic and social levels for the individual and society as a whole.

### **Indication of a major health-economic “problem”**

Over the past century, developed countries around the world have experienced a “longevity revolution”, with a near doubling of life expectancy and a dramatic increase in the numbers of individuals living into their 80s, 90s, and even beyond. The “oldest old” (those over age 85) thus comprise the fastest growing segment of the population, and this group is expected to quadruple in size between 2010 and 2050. “Baby boomers,” i.e. those born after World War II can now expect to live 30 or 40 years beyond the traditional retirement age of 65, giving rise to both challenges and opportunities for individuals and society as a whole (Suzman and Riley, 1985; He and Muenchrath, 2011; Khachaturian, Z.S., 2012 and United Nations, 2007).

The critical health-economic impact of ageing populations worldwide is an unprecedented expansion of consumer demand for healthcare services. Healthcare systems worldwide soon will confront a serious crisis as a result of significant growth of the healthcare market, along with shrinking resources. The magnitude of the problem stems from the convergence of two demographic trends: *a*) increasing lifespan; and *b*) nearly exponential increases in the incidence of disabilities after the age of 65 years (Wimo et al., 2013; CDC, 2011 and UCAtlas, 2000).

Healthcare will be among the issues most radically affected by this demographic revolution. Yet today’s healthcare constructs will be insufficient to respond to tomorrow’s challenges, and merely modifying existing systems for financing and delivering healthcare will not be enough. Rather, novel paradigms and solutions will be needed that transform public policies across multiple domains, from social security, pension and retirement plans to housing and social services to medical and long-term care insurance. And most importantly, investments will be needed in medical and health services research aimed at promoting health and wellness.

The economic consequences of shifting patterns of health status in an ageing society – such as exponential increases in the prevalence of chronic disabilities and prolonged survival with chronic health conditions – are projected to further strain the already fragile economies and/or healthcare financing systems of most countries (Wimo et al., 2013). Governments of OECD countries are rightly concerned

because they pay the bulk of healthcare costs incurred by citizens. In 2011, healthcare spending rose faster than economic growth in all OECD countries (OECD, 2011). Much of that healthcare spending was devoted to diseases for which breakthroughs in diagnosis and treatment are elusive. With life expectancies anticipated to increase significantly across developed and developing nations alike, one of the most important global issues of this century will be the question of how to manage the health and socio-economic impact of chronic disabilities in an ageing population (Delavande et al., 2013 and Lin et al., 2013).

The impact of an ageing society on healthcare systems is multifaceted, which makes it a very difficult issue for policymakers to tackle. The problem consists of multiple complex issues, ranging from health economics and healthcare delivery, to health technology and biomedicine innovation (Khachaturian, 2012). The scale of the predicament will oblige radically different judgments and approaches. Traditional constructs will not be sufficient to address the pending healthcare challenges of an ageing society. There is an urgent need to explore new paradigms or solutions that go beyond attempts to modify the current systems for financing and/or delivering health services. In the light of this pending healthcare challenge, developed countries may need to conduct systematic critical analyses of health policies and priorities in vast arenas of society. These analyses are most urgently needed in the area of the applications of scientific and technological innovations to the delivery of healthcare services and in reducing the economic burden of healthcare. The critical challenge for most countries is how to justify and finance long-term (10 years or more) sustained support to build technical-scientific capacity for research and development (R&D) on health and wellness.

### **Problem of chronic brain disorders (CBD): what are they and why is this so important?**

Chronic disabling conditions in general are major contributors to the economic crisis of healthcare. Chronic disorders, which could involve an organ or any number of physiological-functional systems (e.g. chronic heart condition diabetes, hypertension, arthritis, cancer, stroke, epilepsy and other brain functions), often require prolonged care for decades: thus they consume a proportionately larger share of health resources than other acute conditions. Among all the chronic conditions that have high prevalence in an ageing society, those that impair brain functions – particularly disorders of memory, mobility and mood – have the most deleterious impact on quality of life. Worldwide epidemiological studies show that the prevalence of chronic brain disorders and neurodegenerative diseases, such as Alzheimer's, Huntington's, Parkinson's, and ALS<sup>1</sup> increases exponentially with age, nearly doubling every ten years after the age of 65. Alzheimer's disease (AD) is the most prevalent form of dementia. AD is the perfect prototype chronic disease seeking a solution, a proxy for the larger global healthcare dilemma facing all countries with ageing populations.

### **Why Alzheimer's is a good proxy for CBDs and other age-related disabilities**

Our understanding of diseases such as multiple forms of cancer and diabetes is increasing rapidly, enabling many of these chronic diseases to be prevented, managed, controlled or cured. This is perhaps even truer for infectious diseases, many of which may be prevented through vaccination, or treated with appropriate medication. In comparison with these diseases, Alzheimer's disease remains poorly understood and represents a significant and growing scientific, social and economic challenge to many countries. It may be the ultimate challenge, and is thus a perfect focus for this work.

Alzheimer's disease (AD) is one of a number of ageing-related chronic conditions that will place an enormous burden on healthcare systems because of the need for prolonged care and the resultant high consumption of resources. Thus, focusing on the management of AD as a proxy for the larger problem offers a test case for approaching the complex challenges that need to be addressed, including scientific

and clinical research, technology development, care delivery, public policy, insurance and other financial issues, and psychosocial burdens to caregivers.

This document seeks to outline/identify some of the gaps in knowledge, barriers to progress and opportunities for developing national/international policies to address the grand global challenges of Alzheimer's disease. The specific aim of this report is to provide a basis for, and to stimulate, strategic thinking among policymakers, leading to the identification of areas requiring new work to address the healthcare challenge.

The report seeks to incorporate a wide range of perspectives by considering not only the gaps in knowledge – the limitations of current ideas about pathogenesis, biomarkers, diagnostics and therapeutics - but also the necessity of developing new approaches/paradigms for the discovery-validation of: *a)* surrogate markers for the accurate tracking of disease progression; and *b)* new effective interventions to delay or prevent disease progression. The paper lays out a forward-looking roadmap for potential future policies and joint collaborative R&D initiatives. The report outlines five generic challenges or areas for consideration in developing policies to facilitate a forward-looking future multi-national co-operative R&D initiative. These are: Scientific-technological; Infrastructure and research resources; Administrative-organisational; Regulatory-legal; and Economic-financial (Khachaturian, Z.S., 2012; Khachaturian, Z.S. et al., 2009; Naylor et al., 2012 and Alzheimer's Association Report, 2012).

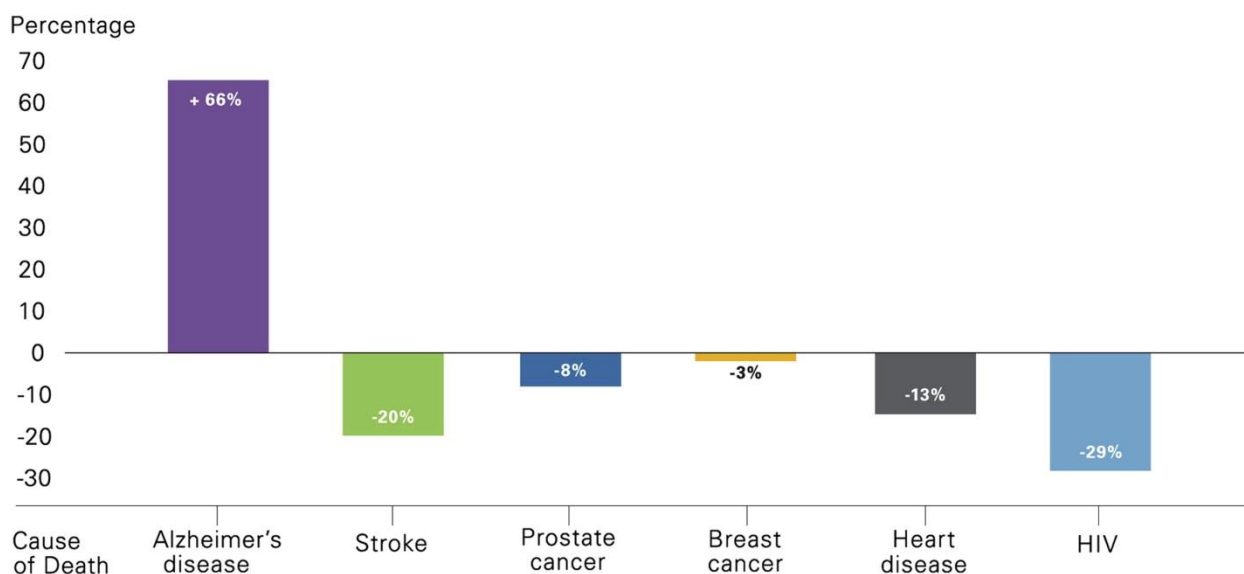


## PRIMER ON ALZHEIMER'S DISEASE: A PROXY FOR CHRONIC BRAIN DISORDERS AND NEURODEGENERATIVE DISEASES

Alzheimer's disease is an irreversible, progressive brain disease that, along with related dementias, affects millions of people worldwide. It slowly destroys brain function, leading to cognitive decline (e.g. memory loss, language difficulty, poor executive function), deterioration of some motor functions, behavioural and psychiatric disorders (e.g. depression, delusions, agitation), and declines in functional status (e.g. ability to engage in activities of daily living and self-care). Eventually, a person with the disease may no longer recognise family and friends and become completely reliant on others for assistance with even the most basic activities of daily living, such as eating.

AD represents a "grand challenge" for the majority of countries (see Figure 1). There is no vaccine, no known prevention strategy, and no cure. The difference between our understanding of Alzheimer's disease and common diseases is reflected in the patterns of mortality associated with these diseases: while mortality from stroke, prostate and breast cancer, heart disease and HIV is decreasing, mortality due to Alzheimer is increasing.

**Figure 1. Percentage changes in selected causes of death (all ages) between 2000 and 2008**



Source: Alzheimer's Association Report 2012, Alzheimer's disease facts and figures, *Alzheimer's and Dementia*, 2012, 8, 131-168, (Permission granted by Alzheimer's Association).

Although the disease can occur as early as the age of 27, these cases are very rare and the symptoms of AD generally start to appear after the age of 60-65 years. The prevalence of the disease increases almost exponentially after the age of 65, doubling every 5 years: 5-7% prevalence in the 60-70 age group; 12-15% in the 70-80 age group, 30-40% in the 80-90 age group; and over 50% in those aged 90 and older.

The demographic trends in the age distribution of populations in all countries project a dramatic increase in the number of people in the older age groups, with the number of over 60s growing from around 600 million at the turn of the 21st century to 2 billion in 2050. The largest increase will occur in the oldest age group of 85 years and older. Nearly four out of every five persons aged 95 and above will be at risk of some form of brain disorder, and the majority of today's baby-boomers are destined to live beyond the age of 85 years. By the year 2050, more than 115 million individuals – up from 36 million today – may be affected by dementia.

Currently, nearly 36 million people worldwide are affected by various forms of dementia including Alzheimer's. In addition to these individuals, 100 million families are affected by the psychological, social or financial burdens of the prolonged in-home personalised care requirements of people with AD or other dementias. If current demographic trends continue unabated, the number of people at risk will double every twenty years. The duration of disability (i.e. the period requiring labour-intensive care) is projected to increase beyond 30 years as progressively healthier cohorts with increasing longevity are affected by the disease (Prince et al., 2011 and Alzheimer Disease International, 2009, 2010 and 2011).

A recent study of approximately 15 000 people over 65 years of age in eight low- and middle-income countries (Mexico, China, India, Cuba, Dominican Republic, Peru, Puerto Rico and Venezuela) found that mild cognitive impairment (MCI) is consistently associated with higher disability, anxiety, apathy, irritability and neuropsychiatric symptoms; but not with depression. This study found that in "low" and "middle" income countries, where the proportion of older people (and people with dementia) in the population is increasing, the prevalence of MCI and related memory disorders ranges from 0.8% in China to 4.3% in India (Sosa et al., 2012 and Alzheimer's Association report, 2012).

The aetiology of AD is not completely understood, but there is growing evidence that the emergence of Alzheimer's is due to the interplay of a combination of factors that include: family history, genetics, comorbid conditions and lifestyle. The relative importance of any one of these factors, in increasing the risk or influencing the expression of the disease, differs from person to person.

Some of the unique characteristics of AD, which mandate new thinking in planning for future priorities in R&D related to technologies in diagnostics and/or therapeutics, include:

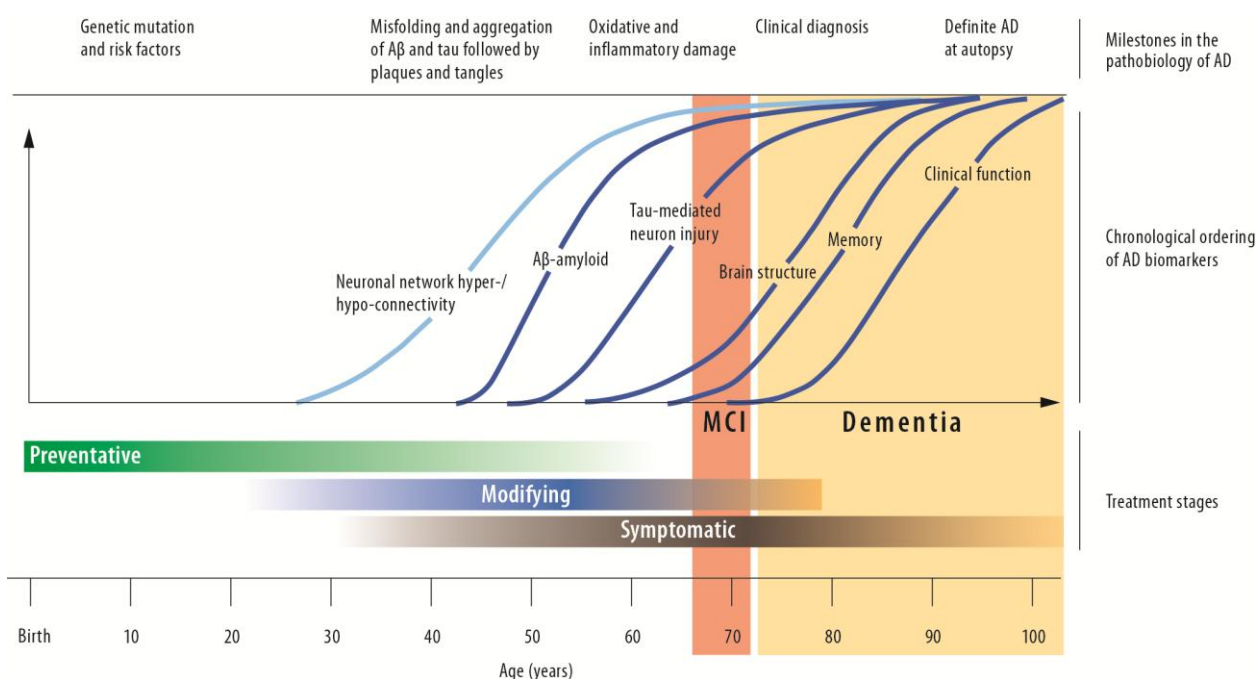
- Alzheimer's is a "syndrome" rather than a "disease". The condition is collectively characterised by a group of symptoms, often consisting of mixed or overlapping pathologies.
- Alzheimer syndrome is heterogeneous with regards to: age of onset of symptoms; patterns or mix of clinical features; neuropathology; biomarkers; response to treatment; risk factors; and genetics.
- The gradual molecular changes in the brain leading to the syndrome appear to start decades before any symptoms can be detected.

These special features of AD also indicate some of the critical challenges in this field (See also the section on "Major opportunities and key challenges" for further details). Some of the critical issues regarding future research or further emphasis include:

- The searching for new conceptual model(s) of the AD syndrome, one which will enable seamless differentiation between affected and unaffected people. The field needs to explain and understand how, in the preclinical stages of the syndrome, transitions from a state of ‘no-clinical signs or normal’ to a phase of ‘detectable pathophysiology’ occur in asymptomatic people at an elevated risk from dementia.
- Current theories regarding the neurobiology of Alzheimer’s disease, which essentially constituted the core of scientific rationale for most therapy development efforts during the last two decades, have proven to be inadequate in generating any effective treatment for this complex brain disease. The unsatisfactory performance of drug discovery-development efforts until now might be due to one or more reasons such as: *a)* wrong drug; *b)* wrong target; *c)* wrong study design; *d)* wrong analytical method; *e)* safety/unacceptable tolerability; *f)* wrong dose; *g)* wrong outcome measure; *h)* wrong stage of the disease; and/or *i)* wrong conceptual model of the disease or mode of action of the therapeutic intervention. Among the plausible explanations for the failure of clinical trials in Alzheimer’s research, the most compelling reason might be the shortfall of the prevailing ideas on pathogenesis to fully explain the complex relationship between the clinical and biological phenotypes of the disease. This uncertainty has begun to recalibrate the thinking about alternative options; many scientists are now ready to re-assess firmly held ideas, assumptions and paradigms of therapy development (Khachaturian, Z.S., 2012; Khachaturian, Z.S. et al., 2009 and Alzheimer’s Association Report, 2012).
- There is a growing awareness in the field that we need different conceptual models for the pathogenesis of the syndrome; new ideas-theories that would account for the issue of: *a)* mixed pathologies in differential diagnosis, clinical studies, and treatment; and *b)* loss of synaptic function. The new models must explain most proximal neurobiological changes that underlie the clinical features of Alzheimer syndrome e.g. viability/integrity of neurons.
- Now there is general consensus among researchers that the neurobiological underpinnings of Alzheimer’s syndrome start many years before the appearance of any clinical signs. Therefore, one of the important scientific challenges is to move the bar for developing new diagnostic (Dx) technologies into the unknown territory of differentiating between the “affected” and the “unaffected” in asymptomatic populations or pre-clinical stages of the syndrome. This will require the discovery-validation of a host of new biomarkers, non-invasive diagnostic tools and computer algorithms for accurate detection or monitoring of the earliest neurobiological processes in pre-clinical phases of the syndrome. The concept of a single biomarker must be replaced with the notion that multiple surrogates might appear and disappear (wax and wane) over the course of the syndrome. Thus prospective R&D efforts on biomarkers must contend with complex interactions across several measurements over-time (Hampel and Lista 2012 and Herrup, 2010).
- The integration of new biomarkers into “diagnostics (Dx)” or “therapeutics (Rx)” technologies in future prevention trials will require new conceptual models for the complete spectrum of pathogenesis of the syndrome, ranging from asymptomatic pre-clinical phase through cognitive impairment in its mild, moderate and severe stages (see Figure 2). For example, such a model should stimulate discovery research for new prospective biomarkers, which would: 1) fully account for the temporal lag between the initiating pathological event and the first appearance of symptoms; 2) provide better explanations for the biological underpinnings of the key clinical features of the disease (e.g. deterioration of cognitive functions); and 3) quantify the therapeutic effect (an index of efficacy) if intended as a surrogate index of “disease progression” (Herrup, 2012 and Shen et al., 2006).

- Clinical trials with “disease modifying agents” or interventions for “prevention” will require: *a)* very large numbers of volunteer study subjects that are asymptomatic and/or have very mild cognitive impairments - MCI (samples sizes in thousands rather than hundreds); *b)* lengthy clinical trials, five-years or longer; and *c)* extremely large investments of funds/resources. The prohibitive costs of future clinical trials on disease modification or prevention will require accurate, sensitive, specific, user friendly and inexpensive biomarkers that track a significant biological process associated (causally) with the syndrome. They will also likely require the integration of large parallel datasets or studies (Hampel et al., 2012 and Khachaturian et al., 2012).

**Figure 2. Chronology of the development and treatment of Alzheimer's disease**



Source: Hampel, H. et al., Karger Gazette No. 72, October 2012 (Permission granted by Karger AG). (Original version of this figure is from: Trojanowski, J.Q. and H. Hampel, *Progress in Neurobiology*, 2011, 95:491-495, Elsevier, pending).

### Magnitude of the health economic challenge: CBD and Neurodegenerative Diseases

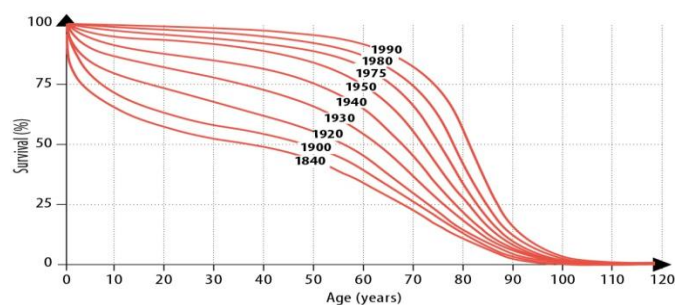
The “problem” of AD embodies the pending global crisis in health-economics: this public health predicament is compounded by the convergence of: *a)* the growing number of older people at risk for cognitive impairment, dementia or some form of CBD; *b)* the rising cost of long-term healthcare; *c)* the devastating toll of these chronic disabling conditions on family caregivers; and *d)* the indirect effects on workforce. The economic consequences of current demographic trends are so enormous that no single country can deal with the problem alone; the pending crisis requires forward-looking public policies to expand multi-national collaborative R&D capabilities and infrastructure to address this grand global challenge.

AD and other neurodegenerative diseases are predicted to directly affect 100 million people by 2050, bringing with them economic and social impacts of such a magnitude as to lead investigators to identify them as one of the most significant challenges of this century, “the number one public-health problem worldwide” (Prince et.al., 2013). Therefore, the question is how to minimise and manage the socioeconomic impacts of chronic conditions globally over the coming decades.

These disorders represent a unique class of disabilities that not only have a profound economic impact but also impose inordinate psychosocial burdens; they impair or severely limit activities of daily living. The most common clinical features of these unremitting brain conditions – progressive functional impairments of cognition and motor skills – eventually lead to total dependence on labour-intensive care to sustain life. Due to increasing lifespan (see Figure 3 and Annex II), the average period of disability for these chronic conditions is gradually being prolonged. At-risk individuals destined to survive beyond the 9<sup>th</sup> or 10<sup>th</sup> decade of life now face the prospects of nearly 30-40 years of disability associated with total dependence for personal care, increasing economic burden and deteriorating quality of life (Khachaturian, 2012; Prince et al., 2013; Council of the European Union, 2008 and Alzheimer's Association Report, 2012).

The 2010 estimates for people with some form of dementia were 35.6 million people worldwide. The projections are that these numbers will nearly double every 20 years, to 65.7 million in 2030 and to 115.4 million in 2050. The true “cost” to society, which includes not only an economic burden but also an inordinate psycho-social toll, will be gigantic (Prince et al., 2013 and Alzheimer's Association Report, 2012). As the numbers of individuals with a longer lifespan increases exponentially, the brunt of the socio-economic problem will be more severe for developing countries, due to the dramatic rise in the older population, by as much as 140% compared with approximately 51% in developed countries by 2030. The worldwide costs of dementia will also soar, exceeding 1% of global Gross Domestic Product in 2010, or USD 604 billion (Prince et al., 2013 and Alzheimer's Association Report, 2012).

**Figure 3. Changes over time in percentage survival rates as a function of age**



Source: Wick, G., *Karger Gazette No. 72*, October 2012 (Permission granted by Karger AG).

CBDs such as AD place an enormous emotional and financial burden on patients and their family and friends. These “informal caregivers” provide the majority of care for people with AD in the community. Informal caregivers often do not identify themselves as such: they are simply a wife, daughter, husband, son, or friend helping out a person about whom they care. However, the intensive support required for a person with AD can negatively impact the caregiver's health and well-being, and their earning potential.

Informal caregivers often report symptoms of depression and anxiety, and have poorer health outcomes than their peers who do not provide such care. When the person with AD moves to a nursing home to receive 24-hour care, the financial costs to families are great. Caring for people with AD also places a burden on health and long-term care systems. Individuals with AD use a disproportionate level of healthcare resources: for instance, they are hospitalised 2-3 times as often as people the same age who do not have the disease. Similarly, while people living in nursing homes are a small percentage of the older

population, nearly half (48%) of nursing homes residents have AD. As the number of people with AD grows over the next two decades, this disease will place a major strain on these care systems as well as on the major funders of this care (Belluck, 2010).

The direct and indirect “cost” of care is conservatively estimated at USD 604 billion a year, or more than 1% of GDP (see Table 1). Costs occur in 77% of the more developed regions of the world (according to the UN classification), with 46% of the estimated prevalence of the disease. While these costs are a major economic burden on the care systems in these developed countries, they are an increasing challenge for developing countries. Developing countries will see the greatest rise in prevalence as the numbers of elderly individuals increase exponentially, rising by as much as 140% compared with approximately 51% in developed countries by 2030 (Belluck, 2010; Prince et al., 2011; Wimo and Prince, 2010; Wimo et al., 2010; Lin and Newman, 2013; Alzheimer’s Disease International, 2009, 2010 and 2011 and Alzheimer’s Association report, 2012).

Advances in diagnostic technologies (e.g., neuroimaging, biomarkers) are promising earlier: *a*) detection of CBDs/identification of AD; and *b*) disease-modifying interventions. These developments and future innovation in diagnostic (Dx) technologies will usher in a paradigm shift in the economics of healthcare and clinical practices. Now there is growing evidence that people with amnesic mild cognitive impairment (MCI) (Lin and Newman (2013)), which affects 10-20% of individuals over the age of 65 years, are at greater risk of developing AD (Khachaturian, 2012; Khachaturian, Z.S. et al., 2009; Nayor et al., 2012 and Alzheimer’s Association, 2012). People with MCI or early stages of a CBD begin to use healthcare services early, thereby incurring costs; however the patterns of these expenditures or resource utilisation have not been well characterised (Belluck, 2010). Although the cost of care in advanced stages of AD has been studied, information on the economic burden during this prodromal stage of AD or MCI is meagre. One of the major challenges for a rigorous economic analysis or modelling of the cost-effectiveness of potential interventions in earlier stages of CBDs or MCI is the gaps in the knowledge base of MCI progression rates and the variables in MCI-related costs (Delavande et al., 2013; Lin et al., 2013 and Lin and Newman, 2013).

**Table 1. Aggregated costs in each WHO region (billions USD)**

	Number of people with dementia	Costs			Total costs	Percent GDP
		Informal care (all ADLs)	Direct costs Medical	Direct costs Social		
Australasia	311 327	4.3	0.7	5.07	10.08	0.97%
Asia Pacific High Income	2 826 388	34.6	5.23	42.29	82.13	1.31%
Oceania	16 553	0.07	0.02	0.01	0.1	0.46%
Asia Central	330 125	0.43	0.28	0.24	0.94	0.36%
Asia East	5 494 387	15.24	4.33	2.84	22.41	0.40%
Asia South	4 475 324	2.31	1.16	0.57	4.04	0.25%
Asia Southeast	2 482 076	1.77	1.48	0.73	3.97	0.28%
Europe Western	6 975 540	87.05	30.19	92.88	210.12	1.29%
Europe Central	1 100 759	8.59	2.67	2.94	14.19	1.10%
Europe Eastern	1 869 242	7.96	3.42	2.94	14.33	0.90%
North America High Income	4 383 057	78.76	36.83	97.45	213.04	1.30%
Caribbean	327 825	1.5	0.78	0.71	2.98	1.06%
Latin America Andean	254 925	0.35	0.31	0.28	0.93	0.43%
Latin America Central	1 185 559	1.58	2.61	2.37	6.56	0.37%
Latin America Southern	614 523	2.36	1.42	1.29	5.07	1.02%
Latin America Tropical	1 054 560	2.17	2.67	2.42	7.26	0.42%
North Africa/ Middle East	1 145 633	1.9	2.05	0.54	4.5	0.16%
Sub-Saharan Africa Central	67 775	0.04	0.02	0.01	0.07	0.06%
Sub-Saharan Africa East	360 602	0.28	0.08	0.04	0.4	0.17%
Sub-Saharan Southern	100 733	0.52	0.11	0.06	0.69	0.24%
Sub-Saharan West	181 803	0.11	0.04	0.02	0.18	0.06%
Total	35 558 717	251.89	96.41	255.69	603.99	1.01%

Source: Alzheimer's Disease International 2010 (Permission granted by ADI).

## **NATIONAL AND INTERNATIONAL EFFORTS TO ADDRESS THE PROBLEM OF ALZHEIMER'S DISEASE – HEALTH-ECONOMIC CHALLENGES**

Over the past thirty years, an expanding global research enterprise has fuelled tremendous progress in understanding the neurobiology of AD and other chronic neurodegenerative disorders. Combined with wider recognition of the pervasive social-economic impact of chronic brain impairments/diseases on modern society, AD research has moved from a position of relative obscurity to the forefront of neuroscience research. Indeed, solving the puzzle of AD has emerged as the grand challenge of our time, with thousands of scientists from around the world that are committed to confront this challenge. Their work has been facilitated by national plans, multi-national collaborations and public-private partnerships (see Annex I). Together, these initiatives provide a firm foundation for developing and validating interventions to reduce the prevalence of AD and other brain disorders (Khachaturian, 2007).

The globalisation of the struggle to find an answer to the AD crisis began in 1984 when the Alzheimer's Association and the National Institute on Ageing convened a meeting in Washington D.C. for the purpose of creating an international forum for linking family caregivers, advocacy groups and support organisations from different countries to share knowledge and experiences. This meeting resulted in the establishment of Alzheimer's Disease International (ADI), which now plays a leadership role in harmonising international awareness and transfer of knowledge about AD.

The annual reports published by Alzheimer's Disease International (ADI) since 2009 document the global burden of AD and summarise worldwide efforts being made to address this crisis (Prince et al., 2011 and Alzheimer's Disease International, 2009, 2010 and 2011). Analysis by ADI indicates that high-income (developed) countries have generally tended to allocate resources for AD prevention and management as an integrated part of their healthcare system, whereas developing countries (with lower GDPs) have tended to emphasise community-based efforts and educational campaigns (Prince et al., 2011).

Now there is a growing consensus in the scientific community that unless the progression of the underlying neurodegeneration can be delayed or prevented, the prevalence of AD and other CBDs, with their concomitant economic-social impact, will continue to grow significantly in the next two decades (Khachaturian and Khachaturian, 2009 and Alzheimer's Association, 2012). However, in spite of the increasing awareness, until recently the worldwide response to the looming threat of catastrophe has been a mixed collage of programmes and plans. The coverage and specific aims of these national plans vary depending on the economic-social- medical-scientific status or needs of countries.

A meaningful comparative evaluation of differing national plans did not exist until a systematic review of such national plans was published in 2011 (Rosow et al., 2011). The authors began by examining national plans in G-20 countries, plans that have been established to develop and co-ordinate research, treatment, and prevention programmes aimed at controlling the pandemic of dementing illnesses. This review defined the concept of a "National Plan" - "a societal recognition expressed either by the government alone or in combination with a national advocacy community that national health policy changes are needed to care and treat individuals afflicted with dementia, prevent or mitigate future cases of illness, and provide support to patients' caregivers".



The review assessed the “comprehensiveness” of plans across five general categories: *i*) call-to-action, meaning a public declaration; *ii*) government/key stakeholder engagement both in creating and implementing the plan; *iii*) allocation of resources to support those government programmes (Rosow *et al.*, 2011); *iv*) provision of funding to accomplish the goals of the programmes (*i.e.* deployment of resources); and *v*) measurement of outcomes and effectiveness after programmes have been put in place. The Rosow *et al.* analysis revealed that the plans differ in their efficacy to bring about policy changes. This evaluation of established and developing policies uncovered several persistent priorities among all national plans, which included: increased awareness, early diagnosis, access to care, improved support services, patient-centred care delivery, research and improved support for caregivers.

The Rosow *et al.* analysis provides information that should better position governments, national medical systems and societies to deal with the impending implications of AD. Their evaluation of national plans concluded that funding is essential for the implementation of all the recommendations laid out within national Alzheimer's Plans. “Plans that have the most success in implementation are those that plan for and budget resources [...] National governments must now make substantial investments to address the prevention, support, and research needs of this disease, and couple these investments with sound policy and legislative initiatives”.

Rosow *et al.*, also noted that “... it is clear that governments cannot do this alone. Advocacy organisations such as ADI, the Alzheimer's Association, and ARDSI<sup>2</sup> have provided leadership in developing many of the national plans. Indeed, public–private partnerships have proven to be essential in advancing initiatives, particularly when resources are limited. Care providers, researchers, physicians, pharmaceutical and biotechnology companies, and individuals with dementia and their families also play important roles in developing plans that are responsive to the individual country's needs” (see Annex 1).

The Rosow *et al.* review clearly indicates the need for some measure of harmonisation of “national plans” particularly with regards to multi-national collaborative R&D initiatives. Public policies emanating from national plans should take into account the complexity and challenges to new programmes which stem from differences in histories, cultures and healthcare delivery systems in participating countries. There is a need to harmonise several disconnected international R&D initiatives to gain more value and increase cost-efficiencies of these on-going efforts. For example, the on-going EC Joint Programming Initiative on AD and other neurodegenerative disorders provides a solid foundation for work to promote capacity building to develop the diagnostic and/or therapeutic technologies for early detection of cognitive disorders (Curtius, 2011 and Rosow *et al.*, 2011).

The 2008 recommendation of the Competitiveness Council of the European Union (EU) to mobilise EU member states to promote research into neurodegenerative diseases, particularly AD is highly relevant to future efforts (Curtius, 2011 and Council of European Union, 2008). Since 2009, the European Commission (EC) has tackled AD and other neurodegenerative diseases by calling for a coordinated joint programming of research efforts to focus on: prevention, diagnosis, treatment and care. The ultimate goal of the EU/EC Joint Programming Initiative on Combating Neurodegenerative Diseases (JPND) is to accelerate: *a*) understanding the causes of these debilitating conditions; *b*) enabling of early diagnosis; *c*) development of new treatments and prevention; and *d*) provision of more effective care to improve the quality of life for patients and caregivers. The EC also expect this programme to develop early, accurate diagnosis tools. In 2011, JPND launched major joint transnational activity between 20 countries to establish collaborative research projects for the optimisation of biomarkers and the harmonisation of their use. Total funding for this programme is more than EUR 15 million for all participating countries, which include: Albania, Belgium, the Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Luxembourg, the Netherlands, Norway, Poland, Portugal, the Slovak Republic, Slovenia, Spain, Sweden, Switzerland, Turkey and the United Kingdom.

There are several indications that the globalisation of AD research, through collaborative multi-site/multi-national projects and public-private partnerships, has played a significant role in the remarkable progress in understanding the neurobiology of ageing and dementia during the last two decades. For example, the collaborative interdisciplinary initiatives mentioned above and those by others funders of international research have played a prominent role in: *a)* promoting rapid translation of knowledge; and *b)* fostering the creation of public-private partnerships for accelerating technology-transfer. Among the relevant international programmes of these entities, many of those of the Alzheimer's Association (AA) provide a good illustrative example.

#### *Investigator Initiated/Peer-reviewed Grant Programme*

A programme which has been in existence since 1982 providing support for research in: basic, clinical, behavioural and social sciences. Since 2000, this programme has become international with over 5 400 scientists from over 50 countries. In 2012, there were over 1 600 individuals from 46 countries who provided more than 3 000 reviews. In terms of '*Funded Grants*' there are nearly 400 active projects funded by the Alzheimer's Association in 20 countries.

#### *Worldwide-Alzheimer's Disease Neuroimaging Initiative (WW-ADNI)*

A programme which has begun to set the stage for the creation of multi-national, collaborative, public-private partnerships. At present the WW-ADNI programme includes participating investigators or institutions from Australia, Canada, Japan, Korea, the United States, Argentina, Brazil, China and Chinese Taipei and various countries of Europe; in the future this effort could be expanded to include additional partners and projects.

#### *Global Biomarkers Standardisation Consortium*

Another example of a multi-national/collaborative effort that has representatives from more than five countries around the world working to standardise cerebrospinal fluid (CSF) biomarkers.

#### *Hippocampal Harmonisation*

A global standardisation effort to measure changes in hippocampus in a standardised manner.

#### *Alzheimer's Association International Conference (AAIC)*

An annual international scientific meeting, which started in 1988, is a gathering of investigators from all parts of the world which provides an opportunity to exchange information and build collaborative networks.

#### *International AD Funders*

A recent coalition convened by the Alzheimer's Association to co-ordinate support of AD research; at present, approximately 20 funding organisations (non-profit and government) are involved.

#### *International AD Research Portfolio*

Another international collaborative project to develop a *Common AD Research Ontology (international)* as a tool for the analysis of the international funding landscape for AD.

#### *Global Alzheimer's Association Interactive Network (GAAIN)*

An initiative to help link scientists around the world with data in a federated manner to advance research.

*International Society to Advance Alzheimer's Research & Treatments (ISTAART)*

A professional society for scientists, physicians and other professionals interested in Alzheimer's/dementia science. This is the first international collegial organisation to represent the interests of all areas of Alzheimer's disease investigation.

*Alzheimer's Association Research Roundtable (AARR)*

An international forum for "public-private" dialogue on forward-looking scientific and public policy issues. The forum convenes three times a year in Washington, DC. The membership includes global representation from virtually all major pharmaceutical and biotechnology companies as well as representatives from government funding and regulatory agencies.

Other initiatives include the European Network of Centres of Excellence in Neurodegeneration:

*The Network of Centres of Excellence in Neurodegeneration (COEN)*

The COEN initiative is based on a joint programme initially agreed between the Canadian Institutes of Health Research (CIHR), the Deutsche Zentrum für Neurodegenerative Erkrankungen (DZNE, Germany) and the Medical Research Council (MRC, United Kingdom) and established in June 2010. The initiative was subsequently joined by the Flanders Institute of Biotechnology (VIB Flanders, Belgium), the Health Research Board (HRB), Ireland/Science Foundation Ireland (SFI), and the Ministero della Salute (MDS, Italy) in October 2011. The Instituto de Salud Carlos III (Spain) and the Ministry of Education, Science, Research and Sport of the Slovak Republic joined the initiative in October 2012. The overall aim of the initiative is to build collaborative research activity in neurodegeneration research across borders, focusing on the critical mass and excellence. COEN is aligned with the broader European Union Joint Programming Initiative in Neurodegeneration (JPND), although it operates as an independent entity.

The multi-national collaborative programmes mentioned here are merely illustrative cases; this list is not a complete or exhaustive compilation of such efforts. For example, an on-going multi-national effort to harmonise not only the process of therapy development but also to address the regulatory challenges on both sides of the Atlantic is the European Union-United States Task Force on AD Trials/CTaD.<sup>3</sup>

In summary, in recent years substantial ground-breaking work has been accomplished in preparations of national plans and the creation of multi-site collaborative consortia. The exciting nature of the scientific puzzle regarding the degeneration of the ageing brain, along with lack of effective intervention to forestall the brain deterioration, has begun to attract scientists from all parts of the world into a now nearly 5000 worldwide cadre of investigators that is committed to solving the puzzle of this grand challenge of our time - the "Problem of Alzheimer".

## **THE GAPS: CHALLENGES IN ADDRESSING THE PROBLEM OF ALZHEIMER'S DISEASE (AD)**

Today, after nearly three decades of struggle to understand the neurobiology of complex syndromes, such as CBD or dementia, the international scientific community is firmly convinced that a focused and well-planned global mission to discover-develop more effective treatments is an essential strategic objective to address the global challenge of AD. They believe, more than ever, that the aspiration of developing a broad spectrum of interventions to reduce the prevalence of disability – by delaying the onset of symptoms, or modifying the progression of the disease, or (eventually) preventing the disease – is an attainable goal within a decade. This common cause binds all stakeholders worldwide. These shared values and opinions of scientists worldwide are having a unifying effect on the thinking of policy makers. For example, several recent plans from the European Union and the United States (e.g. EC/NAPA) call for international co-operation.

Thus the ground is fertile for an international initiative uniting the interests of disparate actors on a single strategic goal: development and validation of interventions to reduce the prevalence of chronic brain disorders such as AD. The scientific community has coalesced around this ambitious undertaking, sensing that the scientific and technical advances of recent years have finally made it possible to achieve this goal. Success, however, will not be easy to achieve. Looking back at some of the national and international initiatives which have grown up in this area, and forward to what might be done in the future, numerous scientific, administrative, regulatory, infrastructure and financial obstacles emerge which will need to be hurdled over the next decade to make this vision a reality (Naylor et al., 2012; Alzheimer's Association, 2012 and NIA/NIH, 2012).

The discussion that follows is a consensus of ideas or priorities for action derived from several sources; published reports or national plans, which can provide the reader with a more detailed analysis and further in-depth coverage of the issues (see references EC; NAPA; NIA/NIH Summit; AA Workgroup Recommendations; LTS'08-'11; UPenn Ware Conference). The areas to be addressed in any future multi-national initiative are organised here under the headings of five generic categories of issues/challenges/opportunities which influence the pace of progress in therapy development. Consideration of the topics covered here should provide the rationale and background material for any well harmonised multi-national plan to address the grand challenge of AD.

### **A. Scientific-technological**

What are the scientific-technical problems that must be solved to address the grand challenge of AD? The two central aspects of this challenge, examples of which are given below, are: *a)* discovery-validation of broad range of technologies for early identification of people with the disease or at risk of developing disease; and *b)* discovery-validation of a number of interventions that would delay or prevent the disease or otherwise find ways to promote or maintain independent functioning for as long as possible.

### ***Advancing knowledge of the neurobiology of Alzheimer's disease***

Despite advances in understanding the neurobiology of AD, there is still much to be learned about the underlying molecular basis of neural systems failure, which manifests as brain-behaviour dysfunction, including dementia. A deeper understanding of these biological mechanisms will be required for the development of effective, targeted treatments that might delay or alter the progression of the disease. Such discovery-to-translational research initiatives, by necessity, will require multi-national co-ordinated efforts (spanning academia, industry, and regulatory agencies) to identify new biological factors critical to the development of AD and, from these factors, to develop potential therapies.

### ***Genomics***

Advances in genomic and sequencing technologies now make it possible to conduct large-scale genome-wide association and sequencing studies. Through international collaboration, the determination of the complete genetic architecture of AD could be achieved. Comparison of data across culturally or genetically diverse cohorts, as donors of representative samples of genetic or other bio-material, can provide critical insights into the underlying pathogenic mechanisms of disease and identify potential therapeutic targets. Such information is essential for the discovery of potential biomarkers as well as for more accurate risk assessment or predictions for developing the disease, including the potential to identify environmental modifiers of disease risk.

### ***Biomarkers***

Research volunteers in pre-clinical or asymptomatic stages of neurodegeneration are needed to develop-validate putative biomarkers as assessment instruments for determining or diagnosing early phases of the disease. These markers, along with other early detection algorithms, could be used not only to identify people at risk to develop disease but also to monitor the progression of the disease and the effectiveness of treatment in changing the course of the disease. Validated tools for accurate identification of asymptomatic people with elevated risk of a CBD are critically needed to address the problem of AD.

Biomarkers of AD measure the underlying pathophysiological processes in the brain that are responsible for observed clinical symptoms. AD biomarkers fall into two descriptive categories, imaging and bio-fluids, and are commonly divided into two mechanistic categories, biomarkers of brain amyloidosis/tauopathy and biomarkers of neurodegeneration/neuronal injury although the necessary further understanding of the earliest biological stages of AD will ultimately yield additional important mechanistic categories of biomarkers.

One of the most significant problems for the emerging field of biomarkers, resulting from diversity of the methods used for the acquisition and processing of data obtained from various patients by different investigators, is the difficulty in comparing findings, interpreting the conclusions reported in papers and generalising from the results of published studies. If the data from studies can be combined in a system with standardised reporting and validation of biomarkers, much more could be gleaned from the research being undertaken across the globe. Additional research would be needed to translate biomarker work that has been successful at individual academic research centres to general clinical practice. The standardisation and validation of biomarkers for regulatory purposes or their transfer to general clinical practice would require large cohorts of well-characterised cohorts, representative of the general population, in all stages of the disease, including preclinical AD (Hampel, Lista and Khachaturian, 2012; Jiang et al., 2011; Hampel, Teipel et al., 1999; Blennow et al., 2010; Hampel and Trojanowski, 2011 and Micheel and Ball, 2010).

### ***Cognitive assessment***

Assessment of cognitive functioning is an essential component of early diagnosis and for evaluating the gradual, progressive decline in mental abilities. Functional assessments are currently used for monitoring disease progression in the three phases of AD: the AD dementia phase, the MCI phase and the preclinical phase. However, most assessment tools today were developed to evaluate patients at the more severe end of the spectrum. As the field is moving towards earlier detection and interventions, novel approaches to cognitive and functional assessment are needed, particularly for the MCI and preclinical phases of disease. Additionally, improved screening methods are essential for identifying individuals in primary care settings who can benefit from treatment at all stages of the disease. Among other things, novel approaches to assessment should be able to leverage computer technologies, as well as web-based methods.

The development-validation-standardisation of the novel instrument/algorithms for assessing cognitive functions will require large cohorts of well-characterised, representative subjects in all stages of the disease, across the adult age range (including those who may have preclinical AD). An international network of researchers working on this area would also be able to examine the relationship between new cognitive and functional measurements in asymptomatic but at-risk people and relevant biomarkers across the spectrum of disease. This effort could provide improved tools for drug development, as well as for identifying those individuals who can benefit from treatment, once improved medications are available (Buschert et al., 2010).

### ***“Systems failure”: A different paradigm for Alzheimer’s disease***

One of the important hurdles to progress in developing effective interventions for AD and other CBDs is the enrichment of therapeutic targets and the pipeline for drug discovery-development. In this regard, research on neurobiology of AD needs to re-evaluate prevailing ideas about pathogenesis and explore alternative conceptual model(s) of dementia, which will: *a*) provide better explanations of the clinical underpinnings of the disease; *b*) identify new therapeutic targets; and *c*) offer the rationale for surrogate markers to accurately track the progression of the disease.

The results of on-going clinical studies have begun to illustrate the limitations of current drug development paradigms and the constraints of current conceptual models of the disease. One explanation for these limited clinical studies may be the failure of prevailing ideas to fully explain the pathogenesis of this complex disease, i.e. the multifaceted relationships between the clinical and biological phenotypes of the disease. The growing doubts about the ultimate success of hitherto promising therapeutic targets provides a compelling reason for exploring the prospects for different or novel conceptual model(s) of dementia. This uncertainty has begun to recalibrate the thinking in the field about alternative options. Scientists in academia and industry are now ready to reassess many firmly held ideas, assumptions and paradigms of therapy development.

Emerging from these efforts may be new models of dementia that take into account both biological and clinical features of the syndrome across the continuum of the disease, from pre-clinical to terminal stages; and which encompasses mixed pathologies that complicate the diagnosis and treatment of patients with dementia. For example, an alternative conceptual model for neurodegenerative disorders based on general systems theory, which incorporates multiple etiologic components as well as the evolution and interactions of pathologic events, could induce a paradigm shift in the approach to therapy development, resulting in multi-modal therapeutic strategies targeting the functionality of the entire system (Khachaturian, 2012; Khachaturian Z.S et.al., 2008; Khachaturian and Khachaturian, 2009 and Alzheimer’s Association, 2012).

Such a multi-genesis model of the syndrome will require drastic changes in hypotheses regarding therapy development. In particular, the discovery of new therapeutic targets intended for prevention will require the adoption of a different way of thinking about the full spectrum of pathogenesis. For example, it is considered that the most proximal pathological events associated with the clinical features of the disease are synaptic failure, dendrite pruning and loss of neurons; thus, new therapeutic targets should focus on protection against synaptic dysfunction or repair/regeneration of the affected neurons. The rationale is that such therapies for prevention or slowing of decline are more likely to succeed when applied in the earlier, pre-clinical (or asymptomatic) stages of the disease rather than at a time when cognitive and functional activities are already significantly impaired. Thus, disease-modifying interventions need to be developed so that they can be delivered decades before the first symptoms appear (Khachaturian, 2012; Hampel et al., 2012 and Hampel and Trojanowski 2011).

To meet the needs for scientific and technological developments in neurobiology, genomics, biomarkers, cognitive assessment and the generalised systems failure illustrated above, there is an opportunity to develop an integrated system to gather, process and compare standardised and validated data to enable the development and validation of interventions to reduce the prevalence of chronic brain disorders such as AD. The infrastructure and research resources likely to be needed to achieve this are considered below.

## **B. Infrastructure and research resources**

What types of infrastructure and resources will be needed to address these science and technology challenges? What are the additional resource needs of the field to facilitate the discovery and validation of biomarkers or technologies for detection of the disease in asymptomatic people or subjects in pre-clinical stages of the disease? What are the capacity building needs for long-term, multi-site, multi-national prevention trials?

The crucial studies needed to validate alternative models and develop therapeutic strategies aimed at slowing disease progression will require an unprecedented level of collaboration as well as substantial new investments in research and infrastructure. Components of this plan that have been proposed and are therefore already in development include the following.

### ***The International Database for Longitudinal Studies on Health Ageing and Pre-Clinical Dementia (IDAD)***

This will be a multi-national shared-resource core facility established to enable the development of new technologies to identify, at the earliest stage possible, those at elevated risk of developing AD, as well as interventions to delay the progression of the disease. The creation of this resource will involve four steps: 1) developing a governance system to oversee and manage the facility; 2) establishing links to other databases and harmonising the data collected in on-going longitudinal studies; 3) establishing a registry of well-characterised, asymptomatic, at-risk volunteers willing to participate in biomarker and/or prevention studies; and 4) establishing an international network of investigators for collaborative discovery research and validation of technologies (Khachaturian, Cami et al. 2009; Khachaturian, Chapman et al., 2010 and Alzheimer's Association, 2012).

The underlying neurobiological changes that occur in the preclinical phase (of the syndrome which eventually is expressed as AD) evolves very slowly over a period of decades. The task of predicting with great accuracy any elevated risks for AD in asymptomatic populations and the mission of discovering/validating new biomarkers or genetic characteristics will require research on very diverse cohorts consisting of large numbers of highly motivated study participants.

Research on AD would benefit greatly from the creation of a comprehensive longitudinal cohort, similar to the "Framingham Study", designed to understand the life-course (early, middle and late life) influence of genetic, lifestyle, environmental and novel (as yet undiscovered) factors on risk for AD. The establishment of such a multi-national collaborative enterprise would require careful integration of longitudinal data from a number of different domains, e.g. behavioural, biological, life-style, genetics, neuroimaging, biomarker and other periodic assessments. This would enable researchers to address some important gaps in the field; for example, the identification of: *a*) factors that may delay or prevent the onset of AD; or *b*) strategies to maintain cognitive function in later life.

A large, comprehensive database such as this could serve the multiple needs of clinical trials on prevention, through epidemiological studies to discover/validate new risk factors, and R&D on technologies for the early detection of neurodegeneration. It could not only improve the cost-effectiveness of long-duration studies but also facilitate the launch of other large-scale collaborative projects such as: *a*)

expansion of Genome-Wide Association Studies (GWAS)<sup>4</sup>; *b*) clinical trials on disease progression or prevention; *c*) characterisation of cognitive ageing; *d*) long-term studies to discover/validate risk factors/biomarkers; *e*) testing of new therapies; *f*) assessment of the impact of “technologies” in home care (e.g. smart-homes); and *g*) assessment of whether early interventions are more likely to succeed when applied before symptoms appear. For example, currently there are several crucial scientific or research questions which cannot be answered even with a very large culturally- and genetically-diverse population-based cohort. A broader database could be used to determine: *a*) the influence of genetic, lifestyle, and environmental factors on the risk and clinical course of AD and possibly other dementias; *b*) the heterogeneity in the prevalence-incidence of AD; and *c*) the profile (genetic/life-style) of subsets of people at greatest risk for developing AD.

### ***Computational biology: An international numerical laboratory as a shared core facility-in silico***

Modelling systems enable the simulation of the entire spectrum of clinical phenotypes of complex brain disease and thereby accelerate the discovery/validation of new generations of therapies. A key limitation of current conceptual models of dementia has been their inability to correlate functional and neurobiological phenotypes. For complex diseases like AD, *in silico* modelling systems enable the simulation of the entire spectrum of clinical and biological (biomarker) phenotypes in order to accelerate the discovery and validation of novel therapeutic strategies.

Harmonisation of different types of data (e.g. clinical, imaging, genetic, neuropsychological, and biological) and the design and execution of *in silico* experiments to generate new hypotheses could be achieved through the establishment of an international numerical laboratory capable of storing large datasets and performing calculations at a high rate. Such a laboratory would utilise several computational models and storage centres to accommodate different types of projects. Based on high performance supercomputing capabilities, this could be especially useful in supporting or adding value to: *a*) on-going studies with data management; *b*) data mining exploration with existing databases; *c*) the applications of systems biology approaches to better understanding of the physiology of disease progression; *d*) genomic studies; and *e*) efforts to identify meaningful early biomarkers (i.e. accurate predictors) by performing factor analysis of large datasets or detecting small changes in continuous data gathered from home-based systems (Khachaturian and Lombardo, 2009 and Khachaturian, Petersen et al., 2011).

### **C. Administrative-organisational**

What are some of the organisational, project management and administrative issues that need to be addressed to facilitate the harmonisation of a multi-national collaborative R&D enterprise? What are some of the actions which could be taken for example, to streamline the selection of research priorities; identify new approaches and organisational structures; and develop new mechanisms of funding research?

Much more can be achieved by harmonising and/or capitalising on the research capabilities, resources, infrastructures, on-going programmes and special scientific strengths of collaborating countries or entities than by acting individually. One road to achieve this is the creation of strategic alliances and public-private partnerships, thereby increasing the engagement of industry.

#### ***Strategic alliances***

No single entity has the necessary scientific knowledge, technical capabilities or resources to develop effective interventions to slow the progression or prevent neurodegeneration in Alzheimer's disease. Collaborative R&D Agreements (CRADA) among all stakeholder e.g. government, academia, industry and voluntary health organisations, such as those used by the US NIH, are a successful model for this type of collaboration. Such alliances require a shared vision – such as the strategic objective of creating technological capabilities to reduce the prevalence of CBDs, and thus the cost of healthcare, within a decade.



Central to such a CRADA is the governance of the partnership-collaboration between government-industry-academia in several different countries. A CRADA for AD should aim to eliminate organisational, administrative, social and legal barriers through appropriate structures and processes for collaboration in R&D (in the pre-competitive arena) in the full spectrum of activities from early discovery to clinical validation of interventions. Competing priorities, missions, agendas and perspectives of stakeholders can lead to programme initiatives that are at cross-purposes or duplicative. A CRADA for AD will also depend on their being public policies for financial incentives (e.g. support for industry partners both to expand research on new treatments and to collaborate with academia and government researchers on these projects).

During the last three decades, some of the most successful scientific programmes have emerged from collaborative multi-site R&D.<sup>5</sup> Given the logistical complexities of harmonising the scientific, organisational and resources requirements of a multi-national plan for AD, the CRADA model for managing such a massive undertaking seems appropriate.

### *Consortia of public-private partnerships*

Research to understand the life-course of the disease process in greater detail in greater detail, beginning decades before symptoms appear, would be greatly advanced by the creation of a comprehensive, diverse, longitudinal cohort similar to that assembled for the Framingham Heart Study. As with Framingham, such a cohort could lead to the identification of genetic, lifestyle, environmental, and other risk factors, as well as biomarkers, which could enable improvements in diagnosis, prognosis, and treatment of AD. Establishing a multi-national collaborative enterprise to build this cohort will require harmonisation of data from multiple domains, including clinical, behavioural, biological, life-style, genetics, neuroimaging, and biomarkers.

Achieving all of these goals would require a collaborative model involving a consortium of public-private partnerships bringing together all stakeholders from industry, academia, public/governmental institutions, regulatory agencies, and advocacy organisations to drive the process of advancing scientific research and supporting the development of new technologies and interventions. This model has been used successfully in advancing research on AIDS while at the same time delivering a series of increasingly effective treatments. Refinement and expansion of the model will be necessary to address the complexity of AD, harness multiple work streams, and determine how best to share risks and rewards in the development of new technologies for early detection, treatment, and prevention. Such partnerships have proven to be effective in aligning priorities, addressing societal challenges that have hindered progress in the past, and sharing the risks associated with the development and validation of interventions. They meld science and business practices by implementing milestone-driven research plans with realistic timelines, developing comprehensive detailed budgets with accountability, and providing professional project management services to keep projects on track. In order to ensure optimal productivity and minimise redundancy, a structure and process for sharing information in pre-competitive space is required, along with sufficient funding to move promising discoveries from the bench to the clinic efficiently. Over the long term, investment in such consortia should result in overall savings as late phase studies are conducted only on well validated and highly promising compounds.

### *Translating research into new technologies*

The concept of an international collaborative multi-site R&D initiative/plan should embrace a systems approach to accelerate the process of 'technology-transfer'. There is a pressing need for more rapid translation of discoveries either in the laboratory or clinic into practical application. Accelerating the process of technology transfer requires enriching the therapy development pipeline with as many high quality options as possible, and then leveraging the most promising findings, including both

pharmacological and behavioural approaches, into the pipeline of validation-development-regulatory approval. International collaboration is essential to establishing a comprehensive and global framework and ensuring alignment of multiple components of the therapy development process, including the recruitment of appropriate patient populations to test the efficacy of new interventions. The OECD countries are uniquely situated to address the need for large, genetically and culturally diverse cohorts to test and validate both putative biomarkers and new treatments.

#### D. Regulatory

What are the regulatory and/or intellectual property issues that need to be addressed to accelerate therapy development? What are the legal hurdles/procedures (concerning drug approval process, intellectual property-patents or market exclusivity) that impede drug development for prevention or technology transfer from basic science to clinical applications? What are some of the changes needed in current law or regulations that would facilitate or provide incentives to develop prevention therapies?

The current regulatory guidelines of the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) originate from two fundamental concerns regarding public safety and well-being, namely, the requirements for demonstrable evidence for: *a*) the safety; and *b*) the efficacy of a new drug (or diagnostic devices/procedure). Other factors that could impact the “value” of an intervention (e.g. quality of life and/or cost-benefit ratio) are becoming an increasingly important part of the decision metrics in the approval of interventions worldwide.

The regulatory issues regarding safety, efficacy, quality of life and cost-benefit ratio of interventions for the mild, moderate and severe stages of AD are relatively straightforward; these topics have been extensively discussed and largely well understood by industry and regulatory agencies. However, the challenges for addressing these issues becomes more difficult without any clear-cut regulatory answers as we move into earlier stages of the disease, e.g. MCI or asymptomatic pre-clinical stages of the disease (Hampel et al., 2012 and Hampel et al., 2010).

Historically the drug approval paradigms of today were developed to safeguard the public while “treating” or “diagnosing” a medically well-recognised or accepted disease. That is, present guidelines presume the existence of well spelled-out criteria for diagnosis and clear cut therapeutic targets or outcome measures that would allow regulatory agencies to determine the efficacy of potential treatments. However, in the emerging era of therapeutics for ‘prevention’ in asymptomatic people with no disease but at risk of contracting a disease, the question is whether the same guidelines can be applied when there is “no disease” or “no diagnosis”? What would be the outcome measure to demonstrate the efficacy of a putative preventive intervention?

The difficulties for blind application of current regulatory requirements to the development of therapeutics/diagnostics for earlier asymptomatic stages of the disease stem from several sources. The assumptions and rationales of current regulatory guidelines to govern ‘treatments’ for a “disease” are not directly applicable to interventions to “prevent” a disease in asymptomatic people (or those in a phase where they do not yet have a “disease”) because:

- There are no criteria or easily identifiable characteristic or clinical features that could be targeted as an outcome measure;
- It is not clear what measure should be used to determine “efficacy”; presently there are no validated surrogate markers to track disease progression.

Consideration needs to be given to the following questions/issues in further developing the regulatory environment around AD and other neurodegenerative diseases:

- What are the regulatory issues that need to be addressed to accelerate therapy development?
- What are the legal hurdles/procedures (e.g. in the drug approval process) that impede drug development for prevention or technology transfer from basic science to clinical applications?
- Are current regulatory laws/guidelines for drug approval (which were designed for interventions of well defined “diseases” with specific “symptoms”) adequate to address the future interventions to ameliorate ill-defined biological processes where the outcome measures are not symptoms alleviation but rather their prevention?
- Is there a need for a paradigm shift in regulatory science *vis-à-vis* “prevention” of disease *vs.* “treatment” of symptoms of a disease?
- If yes, what standards or types of scientific evidence for ‘efficacy’ should be required or specified by regulatory guidelines for prevention drugs e.g. how should clinical trials be organised or what type of trial design will be suitable?
- What are some of the changes needed in current law or regulations that would facilitate or provide incentives to develop prevention therapies?

### E. Economic-financial

What are some of the alternative models to finance a large scale international collaborative R&D initiative and/or very large clinical trials for prevention of AD and other CBDs? Are there any paradigms for financing such a massive public-private enterprises that could be adapted to support, for example, a 10-year multi-nation R&D effort regarding Grand Global Challenge of Alzheimer’s Disease?

Current paradigms for therapy development, based on purely competitive research models (i.e. separate groups working alone) have not delivered effective therapies for complex brain disorders, such as AD and other CBD. A different paradigm, relying on co-ordination of knowledge, expertise and resources of multiple collaborators-partners in a non-competitive R&D environment, for validating potential therapeutic targets would require a multi-national collaborative effort.

Multi-national collaborative R&D endeavours require the development of detailed multi-year operating plans including a rigorous financial analysis. Critical analysis/evaluation is required of various models for financing a multinational project where all partners share equally both the “risks” and “benefits” of the entire enterprise, the aim being to develop an appropriate mode for financing. In parallel, it would be necessary to develop appropriate governance (organisational/administrative) paradigms to facilitate the seamless interplay of business and science in the therapy development process.

There are various existing models of joint ventures between academic and industrial labs which can be considered. These partnerships include:

- The Cardiovascular Health Study (CHS), a 10-year study of risk factors for the development of heart disease and strokes in adults over the age of 65. Beginning in 1989, 5 201 participants were enrolled at four locations. In 1992 an additional group of 687 primarily African-American subjects were enrolled and a cognition sub-study and magnetic resonance imaging were added to the protocol.

- The Multi-domain Alzheimer's Prevention Trial (MAPT) underway in France is investigating whether cognitive decline can be slowed through a combination of omega-3 fatty acid supplementation and multi-domain treatment (physical and cognitive exercise, nutrition, and social stimulation). Over 1 600 frail elderly volunteers have been recruited at university hospital centres and memory clinics in Toulouse, Bordeaux, Limoges and Montpellier.
- The German Competence Network on Dementia is collecting extensive longitudinal neuropsychological, clinical, neuroimaging, genetic, and biomarker data over on a group of 3 327 cognitively normal (at baseline) subjects over the age of 75 as well as 2 113 subjects with early signs of AD or MCI. Subjects are enrolled at university research centres and memory clinics in six urban areas.
- The Consortium of Canadian Centres for Clinical Cognitive Research (C5R) has formed a clinical trials network with 33 clinics.
- Spanish investigators are studying the effects of environmental exposure on neural development in a four-year study of 4 000 children. Investigators are seeking early markers of neural development and metabolic syndrome, and are also studying whether air pollution affects cognition by increasing oxidative stress and neuroinflammation.
- The Alzheimer's Disease Genetics Consortium, funded by the National Institutes of Health, is conducting a Genome Wide Association Study (GWAS) to identify genetic factors associated with AD in well-characterised cohorts from various studies, including the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort. Data are included from 2 000 cases as well as 2 000 controls.
- The European Community Concerted Action on the Epidemiology and Prevention of Dementia Group, established in the early 1990s, has brought together numerous population-based cohorts throughout Europe. The collaborative efforts of this group may be useful in creating EU-NA collaboration.

This section has laid out some key challenges in addressing the Alzheimer's problem. In the next section, we explore options to address those challenges.

## POSSIBLE WAYS TO ADDRESS THE GLOBAL ALZHEIMER'S DISEASE CHALLENGE

### A global approach to a grand challenge

The scope and scale of the Alzheimer “Problem”, as a prototype for a host of other chronic disabling conditions, call for a global response. Leaders in governments, business and academia recognise the need for a well-coordinated strategic plan to address this grand global challenge for healthcare systems. The consensus among all stakeholders is that the present worldwide technical/scientific capabilities, infrastructure and resources for R&D need to be strengthened. There is a pressing need for global engagement and commitment to a significant expansion of and investment in global R&D capabilities/resources dedicated to reduce the duration of chronic brain disorders and/or numbers of people at risk for these conditions. These financial outlays should be coupled with sound legislative/policy initiatives to foster public-private partnerships and broader engagement. History has proven that collaboration among academic investigators, government, and pharmaceutical and biotechnology companies is an essential ingredient in advancing such bold initiatives, particularly when resources are limited.

The response to this global challenge to healthcare systems is to create a forum and a mechanism whereby all countries and stakeholders could collaborate and harmonise to delineate specific actionable initiatives(s) and projects for a well-coordinated multi-national strategic plan to address the problems of CBD such as AD and other chronic conditions of an ageing society. The formulation of a harmonised strategic plan could provide a common anchor for new policy work, which would facilitate countries to develop strategies for: *i*) sustained investment in science and technology (in order to build-up their own R&D capabilities and competitive position *vis-à-vis* global research enterprises); *ii*) building-up resources and infrastructure for R&D; and *iii*) expanding the pool of scientific and technical human resources. One of the outcomes of this work will be an improved R&D infrastructure for AD. It is also expected to reduce the social and economic impacts of AD through the development of scientifically sound and validated policies to support the proposed multinational strategic plan. Given the R&D basis of this work, it is anticipated that the outcomes of this work would be widely applicable to other complex diseases and unmet health needs.

### Rationale for a harmonised plan to address AD

The primary premise for a harmonised plan to address the global challenge of AD is that the cost and duration of therapy development must be drastically reduced and made more cost-effective. Very long clinical trials (15-20 years) are needed to demonstrate the efficacy of any potential preventive therapies, trials which are also extremely costly. Time and cost are significant barriers which need to be overcome in developing prevention therapies.

In order to make ‘Prevention’ a realistic strategic goal, the cost and period for therapy development must be shortened to about 3 to 5 years. This shift from the current paradigm of therapy development will require: *a*) discovery and development of new Dx technologies, e.g. surrogate markers; *b*) validation and efficacy studies of new Dx technologies (e.g. putative surrogate markers) for early detection on very large

numbers of well diversified volunteers from asymptomatic populations; and *c*) registration of new Dx technologies for general clinical use, with bodies such as the Food and Drug Administration (FDA) and European Medicines Agency (EMA), by demonstrating positive results from validation-efficacy studies with large, diverse populations.

The two essential needs for developing prevention therapies are:

- i*) the creation of a multi-national shared R&D resource to facilitate the development-validation of new technologies and biological markers that can serve as proxies (i.e. surrogate markers) for the biological process that leads to dysfunction;
- ii*) the formation of an international network of collaborators to identify and enrol individuals in the earliest stages of the disease into a multi-purpose international database for longitudinal studies.

To integrate biomarkers into the future development of diagnostic and/or therapeutic technologies, the proposed approach would be to focus on:

- a*) creating the essential R&D infrastructure as an international shared resource;
- b*) building the organisational structure for managing such a multi-national shared resource;
- c*) establishing a global network of collaborating investigators to help build and utilise the shared research resource.

One of the critical requirements for rapid translation of putative biomarkers into useful tools for diagnostics and regulatory requirements is the availability of a comprehensive longitudinal database on large and diverse cohorts of: *a*) healthy ageing; *b*) people at elevated risks (genetic/life-style/co-morbid conditions) pre-clinical/MCI/Mild to Moderate AD, etc.

The conceptualisation and planning of the organisational structure and functional capabilities of this type of an international shared research resource is a necessary first step. The objective of the multi-user R&D core facility is to create a comprehensive international database for longitudinal studies. The aim is to create a mechanism or system for recruiting large numbers of volunteers to meet the needs of multiple projects and studies for research subjects; rather than a narrowly structured resource to serve the needs of a single study or fill the requirements of a particular hypothesis. Working with well-diversified large numbers of asymptomatic cohorts will enable the launch of multi-site collaborative studies on: discovery-validation of biomarkers, factors that lead to successful ageing, complex mechanisms (phenotype-genotypes interactions) underlying diseases of the ageing brain. Such a multi-use R&D resource will provide the world's scientific community an unprecedented opportunity to plan and execute a wide range of population-based studies to solve critical issues related to public health, ageing and/or brain disorders.

The multi-national research resource could be readily built on current programmes and initiatives, leveraging existing resources to meet the overarching goals of a multi-national collaborative programme. The aim would be to create a level playing field whereby all countries (rich-poor, developed-developing, all levels of technical-scientific strengths-weaknesses) would be able to contribute and benefit from the resource.

It is generally known that by the time a person is diagnosed with dementia, the disease has already caused neurodegeneration of vast areas of the brain e.g. hippocampus. Yet the necessary technologies to measure important antecedent conditions such as dendrite and/or synapse loss are not yet available. The crucial challenge for 'prevention', as a strategic goal, is the need to develop our capabilities for accurate prediction of who is likely to develop incident cases of dementia among asymptomatic people in the general population. Technologies for accurate detection of people at risk can lead to strategies for preventing the development of key risk factors and therapies to slow the progression to clinical dementia.

This will require the application of not only existing technologies (e.g. imaging, biomarkers, and genetic risk factors) to younger people, but also the development of new technologies to extract as much information as possible from very early indicators, to predict: *a)* an individual's disease trajectory; and *b)* how a putative treatment might alter that trajectory.

The multi-factorial nature of the disease will require sophisticated computational capabilities for pattern analysis of various indicators, as has been the case in genomics and proteomics studies. The goal is to identify the relevant set of indices so that when an intervention becomes available, appropriate individuals can be selected to test the effectiveness of that intervention. As the tools or biomarker measures identifying neurodegeneration in earlier stages of the disease become available they will play an important role in advancing knowledge about fundamental mechanisms that underlie dementia; why synapses are being lost, and why dendrites are pruned in specific ways. Such an understanding is critical if we are to develop effective preventive strategies.

### **A harmonised multi-national public policy focus**

The thinking behind several national plans for AD is that initiating early interventions in the MCI phase could not only improve the health of patients but also the well-being of caregivers; also early interventions could possibly offset certain costs. The database/information and technology for accurate forecasting of how early treatment may influence downstream costs would enable better targeting of healthcare services throughout the AD continuum. Lin and Neumann (2013), have indicated that “Many uncertainties exist about the potential cost-effectiveness of early detection and therapy for MCI. Economic analyses are needed to account for the impact of interventions on increased time in the MCI state, and consequences for patient and caregiver productivity and the long-term cost. A new comprehensive AD simulation model, which includes an MCI state, could help researchers assess the economic impacts of early diagnosis and treatment, and to inform coverage and reimbursement decisions of new interventions. The model also can help clinicians characterise various progression scenarios, which may assist patients and their families with disease planning [...] Many payers now use economic data in addition to safety and efficacy measures for drug and medical reimbursement decisions. It is important for payers, providers, and policy makers to understand the economic aspects of MCI, as they will invariably confront invariably decisions about the costs and benefits of new tests, treatments, and other management strategies for the condition. Economic data can be used not only to improve efficiencies but also to enable informed management decisions, such as identification of patients who are most likely to benefit from early interventions” (Lin and Neumann, 2013 and WHO, 2005).

The creation of an international comprehensive database for longitudinal studies and analysis should enable or facilitate future economic analysis by incorporating new information on patients into larger databases and linking administrative claims and electronic medical records to study cost consequences of early Dx and Rx. Such analyses should help payers, providers, and policy makers make more informed decisions about the costs and benefits of new tests, treatments, and other management strategies for the condition.

To this end, the immediate need is to develop well-harmonised multi-national public policies to pursue a common strategic objective, namely to reduce the numbers of people at risk and the costs of care. The most effective solution to the grand challenge will require expanded investments in R&D - building-up scientific capabilities-infrastructure - to enable multi-nation collaborative projects aimed at decreasing the magnitude of the problem by:

- Prevention - reducing the number of people with disability or at risk,
- More effective interventions – shortening the duration of disability,
- Lowering the cost of care – new models of care (Khachaturian, Z.S., 2012 and Alzheimer's Association, 2012).

The central thrust of the proposed action plan calls for the launch of a collaborative multi-national R&D effort; with the tactical and measureable goal of reducing the prevalence of AD and other CBDs that affect memory, movement, and mood (e.g., reduce by 50% within five years). The initiative is based on the premise that a modest delay of five years in the onset of brain disability will reduce the cost and prevalence of these chronic conditions by half; this view is widely shared by experts in the field. The rationale is that delaying the onset of disabilities will offer the most cost-effective long-term solution to the looming healthcare crisis (Khachaturian and Khachaturian, 2009 and Alzheimer's Association, 2012).

The creation of multi-national R&D networks; working collaboratively – in the pre-competitive arena – towards developing validating novel technologies for reducing the prevalence of chronic brain disorders within a decade would require massive mobilisation of global resources to enable:

- expansion of global research capabilities, resources, and infrastructure
- support and funding of discovery-validation-development of a broad spectrum of:
  - Technologies for accurate detection of people at risk;
  - Interventions targeted towards disease modification and/or prevention of neurodegeneration.

The justification for substantial infusion of public funds into “big-science” (e.g. human genome project) will require: *a)* sound policy support; *b)* credible scientific rationalisation; and *c)* a realistic strategy and plan for effective utilisation of sustained investments in research over a long period (e.g. a decade or more).

The challenge of developing a multi-national consensus on a comprehensive scientific agenda is a daunting enterprise that will require the concurrence of stakeholders with varying perspectives or competing priorities.



## CONCLUSION: WHAT COULD BE ACHIEVED BY ADDRESSING THESE CHALLENGES?

The core issue for the pending global health-economic crisis is how to reduce the prevalence of chronic disabling conditions, thus significantly reducing the prospective cost and demand for prolonged health services. The solution of this grand challenge will require the development of the necessary knowledge and infrastructure for discovery, validation and development of new more effective technologies for early and accurate detection and identification of people at elevated risks and interventions to delay or prevent the onset of disabling conditions.

This grand challenge should be seen in the wider context of the changing demographics resulting from increasing life span and reducing fertility, with the prediction that by the middle of the century over 40% of people in G-20 countries and approximately one-third of the global population will fall into the category of “elderly” people. By working towards achieving a greater level of health in the ageing population, it will be possible to help people to have productive and fulfilling longer lives, reducing the healthcare burden, increasing economic productivity and creating a better social environment for all, with biotechnology contributing significantly to that goal.

The following are some illustrative examples of what could be achieved by addressing the gaps and challenges identified in this report:

- Expand and build-up R&D capacities – better or more complete understanding of the neurobiology of Alzheimer disease and dementia will allow the discovery of new, perhaps more effective, therapeutic targets and interventions.
- The formulation of new conceptual models of the disease will increase the prospects of discovering disease modifying treatments by enriching the pipeline for potential therapeutic agents.
- Building upon current programmes and initiatives and leveraging existing resources to meet the overarching goals of a multi-national collaborative programme.

Strengthening international R&D capabilities, especially by the creation of a shared research resource, will provide multiple benefits, for example, by supporting:

- Longitudinal studies (on asymptomatic people at elevated risk) designed to discover and validate biomarkers.
- Epidemiological studies to assess potential risk factors.
- Clinical trials and studies to determine the efficacy of potential disease-modifying therapies;
- Validation of biological markers for early detection of neuro-degeneration.
- ‘Living laboratories’; for research and development in telemedicine and other health technologies.

- Testing and developing new models of technology-based care and validation of interventions to reduce chronic disability.
- The study of interactions among risk factors and/or genetic variables and to help overcome one of the major barriers to clinical trials/studies, that is, the recruitment of subjects;
- Creation of the infrastructure needed to conduct early detection and prevention studies by identifying early risk factors, biomarkers, genetic markers, and other data that will allow for predictions of an individual's likelihood of developing dementia;
- Provide resources that researchers can use to test hypotheses or generate new hypotheses related to causation and intervention. These resources include both new instruments that will need to be developed and validated, and large, diverse cohorts of well-characterised individuals to participate in trials of new instruments and interventions.
- Use these resources and infrastructure in the development of interventions that will delay, ameliorate, or change the course of AD, or prevent the disease altogether.
- Attract more young investigators to the field by making these resources broadly available and by providing access to the leading scientists in the field from around the world.

## NOTES

- <sup>1</sup> Amyotrophic lateral sclerosis (ALS) often referred to as Lou Gehrig's Disease.
- <sup>2</sup> Alzheimer's and Related Disorders Society of India
- <sup>3</sup> Led by Bruno Vellas, Toulouse and Jacques Touchon, Montpellier - [www.ctad.fr](http://www.ctad.fr)
- <sup>4</sup> <http://gwas.nih.gov/>
- <sup>5</sup> Since 1978 the National Institute on Ageing (NIA) at the National Institute of Health (NIH) established an extensive network of collaborative multi-institutional programmes of at academic institutions. These programmes, which have been extremely productive have included - AD Centres (ADCs), Consortium to Establish a Registry for AD, AD Cooperative Study (ADCS), AD Drug Discovery Program, National Alzheimer's Coordinating Centre, and National Cell Repository for AD, and ADNI.

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## ANNEX I – LIST OF NATIONAL PLANS TO ADDRESS ALZHEIMER'S DISEASE

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**ANNEX II – EXAMPLES OF LONGITUDINAL STUDIES OF AGEING IN EUROPE (ORDERED BY START DATE)**

<b>Study</b>	<b>Country</b>	<b>Start</b>	<b>N (Baseline)</b>	<b>Age</b>
Iceland Birth Cohort Study	Iceland	1957	3704	61-64
Bonn Longitudinal Study of Ageing (BOLSA)	Germany	1965	221	60-75
Gothenburg Study (Göteborg)	Sweden	1971	1148	70
Southampton Ageing Project (SAP)	United Kingdom	1977	340	65+
Bangor Longitudinal Study of Ageing (BLSA)	Wales, United Kingdom	1979	534	65+
Melton Mowbray Ageing Project	United Kingdom	1981	3000	75+
Nottingham Longitudinal Study of Activity and Ageing (NLSAA)	United Kingdom	1983	1042	65+
Cambridge City over 75's Cohort (CC75C)	United Kingdom	1985	2165	75+
Personnes Agées Quid (PAQUID)	France	1987	3777	65+
Kungsholmen Project	Sweden	1987	1810	75+
LUND 80+	Sweden	1988	211	80
ALPHA	United Kingdom	1989	5222	65+
Pamplona	Spain	1989	1127	70+
AMSTEL	Amsterdam	1990	4051	65–84
Berlin Ageing Study (BASE)	Germany	1990	516	70-105
Rotterdam	The Netherlands	1990	7983	55+
Medical Research Council (MRC) Cognitive Function and Ageing Study (CFAS)	United Kingdom	1991	13004	65+
Etude du Vieillissement Artériel (EVA)	France	1991	1389	60-70
Vantaa 85+	Finland	1991	553	85+
Italian Longitudinal Study on Ageing (ILSA)	Italy	1992	5632	65-84
Longitudinal Ageing Study Amsterdam (LASA)	The Netherlands	1992	3017	55-85
Maastricht Ageing Study (MAAS)	The Netherlands	1992	2043	24-81
Zaragoza	Spain	1992	1080	64+
Odense	Denmark	1993	3346	65-84
Longitudinal Study of Ageing Danish Twins (LSADT)	Denmark	1995	2401	75+
The German Ageing Survey	Germany	1996	5000	40-85
Leipzig Longitudinal Study of the Aged (LEILA 75+)	Germany	1997	1378	75
English Longitudinal Study of Ageing (ELSA)	England	1998	12100	50+
The Danish 1905-Cohort Study	Denmark	1998	2262	93

In Chianti Study	Italy	1998	1453	20-102
3-City Study	France	1999	9294	65+
ZARADEMP	Spain	2000	4803	55+
The Swedish National study of Ageing and Care (SNAK-K)	Sweden	2001	3089	60+
The Norwegian Life Course, Ageing and Generations Study (NorLAG)	Norway	2002	5589	40-79
Newcastle 85+ Study	United Kingdom	2006	1042	85
CFAS II	United Kingdom	2008	Recruiting	65+
CFAS II-Wales	Wales, United Kingdom	2011	Planned	65+

Source: Brayne C, Stephan BCM, Matthews FE. Perspectives: A European perspective on population studies of dementia. *Alzheimers Dementia* 2011; 7: 3–9

## GLOSSARY

AA	Alzheimer's Association [US]
AAIC	Alzheimer's Association International Conference
AARR	Alzheimer's Association Research Roundtable
AD	Alzheimer's Disease
ADC	Alzheimer's Disease Centre
ADCC	Alzheimer's Disease Core Centre
ADCS	Alzheimer's Disease Cooperative Study
ADI	Alzheimer's Disease International
ADNI	Alzheimer's Disease Neuroimaging Initiative
ADRC	Alzheimer's Disease Research Centre
AIDS	Acquired immunodeficiency syndrome
ALS	Amyotrophic lateral sclerosis /or/ motor neuron disease /or/ Lou Gehrig's disease
CBD	Chronic Brain Disorders
CRADA	Collaborative R & D Agreement
CTAD	Clinical Trials on Alzheimer's Disease
Dx	Diagnostics
EC	European Commission
EMA	European Medicines Agency
EU	European Union
FDA	US Food and Drug Administration
GAAIN	Global Alzheimer's Association Interactive Network
GDP	Gross domestic product
GWAS	Genome Wide Association Study
HD	Huntington's disease
HIV	Human immunodeficiency virus - a lentivirus
IDAD	International Database for Longitudinal Studies on Health Ageing & Pre-Clinical Dementia
ISTAART	International Society to Advance Alzheimer's Research & Treatments
JPND	Joint Programming Initiative on Combating Neurodegenerative Diseases

MCI	Mild cognitive impairment
NAPA	National Alzheimer Project Act
NIA	National Institute on Ageing
NIH	National Institutes of Health
OECD	Organisation for Economic Cooperation and Development
PD	Parkinson's disease
R & D	Research and Development
Rx	Therapeutics
UN	United Nations
WG	Workgroup
WW-ADNI	Worldwide-Alzheimer's Disease Neuroimaging Initiative