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Global Action to Drive Innovation in Alzheimer's Disease and Other Dementias

CONNECTING RESEARCH, REGULATION AND ACCESS

OECD

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FOREWORD

The OECD has been providing support to its member countries and other stakeholders such as the WHO, the World Dementia Council (WDC), and the G7 Countries on issues related to global health challenges. The OECD Working Party (WP) on Biotechnology, Nanotechnology and Converging Technology (BNCT), in line with its current Mandate and under the Programmes of Work and Budget (PWB) for 2013-14 and 2015-16, pursued analytical work on the assessment of policies to support healthy ageing and to accelerate a global paradigm shift in biomedical research and health innovation for Alzheimer's disease and other dementias.

The WP on BNCT, in partnership with the Swiss State Secretariat for Education, Research and Innovation (SERI); The Global CEO Initiative on Alzheimer's Disease (CEOi); and Alzheimer's Disease International (ADI), convenes an annual invitation-only Leadership Workshop to review the progress, barriers and needed actions to advance on the path to identifying a means of prevention and effective treatment of dementia by 2025, the goal embraced by the G8 Health Ministers in December 2013 and confirmed by the Call to Action issued at the First WHO Ministerial on Dementia in March 2015. A particular focus was placed on the persisting challenges and barriers to the introduction of new diagnostics and therapies into markets – developing innovative strategies for more regulatory flexibility and global access to future therapies. This report is a summary of the second Lausanne Workshop 'Global Action to Drive Innovation in Alzheimer's disease and other Dementias – Connecting Research, Regulation and Access' held 15-16 December 2015 in Lausanne, Switzerland.

Given the success of the Lausanne Workshops, stakeholders have urged organisers to continue the "Lausanne Dialogue" as a platform for policy makers, academia, the pharmaceutical industry, patient and caregiver organisations, funders, payers, and the civil society. The OECD and its collaborators are well placed to convene actors in Alzheimer's disease and other dementias in order to design the shared actions needed to be taken to achieve a shared solution to the global society posed by the growing health and economic challenges of Alzheimer's and other dementias.

A special note of appreciation is extended to Ms. Hilary Doxford (Alzheimer's Society, Research Network Volunteer; Member, World Dementia Council) and her husband Mr. Peter Paniccia who generously supported the workshop. Their insights into the needs and perspectives of those with dementia and their caregivers have been a valuable contribution to the discussions and outcomes of the workshop. Any ensuing event will be built on the critical role of persons with dementia in research, drug development and universal access to future diagnostics and therapies.

TABLE OF CONTENTS

EXECUTIVE SUMMARY AND KEY INSIGHTS

The second Lausanne Workshop of December 2015 reviewed the policy and stakeholder actions needed to accelerate biomedical research and health innovation for Alzheimer's disease and other dementias. The agenda featured developments in regulatory and access pathways for potential innovations in dementia. Participants discussed the perspectives of regulators and payers, specifically the evidence and tools needed to support regulatory and payer evaluation of innovations. A particular focus was placed on the large and growing societal implications of Alzheimer's disease and the heightened urgency to define sustainable access strategies for future diagnostics and therapies.

Lessons learnt from the first Lausanne Workshop "Enhancing Translational Research and Clinical Development in Alzheimer's Disease and other Dementias: The Way Forward", 2014, Switzerland, spurred a cross-sectoral discussion about how to incorporate the paradigm shift from therapeutic research in established dementia to pre-clinical stages into research policies, adequate clinical trial designs, and regulatory processes. Policymakers and the research community have an integral leadership role to foster collaborative efforts to deliver the best available science for evidence based policies and approval processes.

There is consensus across all stakeholders to move from global agenda setting in Alzheimer's disease to action oriented programmes and implementation. The medical, societal and economic dimensions of the dementia challenge require a comprehensive, scaled and urgent response through joint action in risk reduction (nutrition and lifestyle), diagnosis and treatment (early detection and diagnosis, symptom management, disease modifying and combination therapies), and access (clear regulatory pathways, manufacturing, sustainable market schemes). The following conclusions can be drawn from the Workshop.

Progress made: New innovations in the diagnosis and treatment of Alzheimer's disease and other dementias are in sight. A significant number of candidate therapies are in late stage trials and, assuming successful trials and approval, are on a path to be on market in the next five years. At the time of the Workshop there were approximately 41 potential therapies in Phase 2 trials and about 22 in Phase 2/3 and Phase 3 trials.[i] The Lausanne Workshop has been a showcase of how scientific advances, new regulatory and access policies, and persistent frameworks for collaboration are creating actions to address the barriers to advancing innovative therapies for Alzheimer's and other dementias. For example:

- Infusion of additional public investment in Alzheimer's research in the US and Europe as well as the creation of the innovative public-private Dementia Discovery Fund to invest in preclinical and early-stage clinical research;

- Set-up of the 'Integrated Development Initiative' led by Dr. R. Long to increase the efficiency of clinical trials in Alzheimer's disease through an international coalition of regulatory agencies;

- Initiation of the FDA-EMA inter-agency and sponsor dialogue and qualification advice to enable efficient parallel submissions for Drug Biomarker Qualification or Clinical Outcome Assessment Qualification;

- Formation of the Global Alzheimer's Platform (GAP) Foundation to accelerate the enrolment of secondary prevention trials through an innovative, highly efficient approach to identify, evaluate, and enrol appropriate preclinical and prodromal trial candidates and through a standing network of high-performance trial sites;

- Development of flexible, more efficient trial designs (e.g. Adaptive POC Platform Trials, IMI-EPAD project) to evaluate multiple treatments and combinations of treatments, in parallel;

- Conduct of deep and frequent phenotyping cohort studies such as CCNA and CIMA-Q to fill knowledge gaps and to complement volunteer registries for large proof-of-concept trials;

- Initiation of the 'Health e-Brain' study to investigate caregivers' stress levels and potential negative mental and physical effects in people who regularly provide care for dementia patients;

- Launch of key projects that will harness the power of "big data" in both the EU, led by The Innovative Medicines Initiative, and the US, led by The Global CEO Initiative on Alzheimer's Disease;

- Commitment of the World Health Organization (WHO) Member States to propose the adoption of a resolution on dementia at the Sixty-ninth World Health Assembly 23-28 May 2016;

- Commitment of the OECD to a continuing collaboration to conduct further annual meetings of the Lausanne Dialogue in 2016-17.

Defining the barriers: Participants concluded that despite the significant progress made and the recent increase of public and private support, major obstacles remain along our path to both prevent and effectively treat Alzheimer's disease by 2025: 1) Funding gaps should be addressed through partnerships between governments, private and philanthropic investors. Investment gaps in preclinical and translational research should be closed through a concerted approach to strengthening basic research and sharing financial risks during early clinical development; 2) Recruitment for clinical trials remains a major bottleneck due to difficulties in identifying and characterising the right volunteers at an economically sustainable cost. Delays in trial recruitment hampers research advancement, threatens internal uniformity and consistency, raises concerns about the reliability and generalizability of results, and increases costs; 3) Inadequate links between the research community and people living with dementia lead to incomplete information about the needs and expectations of patients in clinical research, diagnosis and symptomatic treatment; 4) Lack of globally accepted and operationalised definitions of preclinical and early Alzheimer's affects (regulatory) policy development; 5) Disparate views between innovators, payers, governments, businesses and societies on what constitutes therapeutic and diagnostics value creates regulatory and access uncertainty.

Applying lessons learnt: Experiences in other disease areas, such as HIV/AIDS, cardiovascular disease, Parkinson's disease, cancer, and some rare diseases offer valuable lessons about how to overcome barriers being encountered in Alzheimer's disease and other dementias. The example of HIV/AIDS has shown that agreed biomarkers, prioritisation, adequate funding, innovative and collaborative management, collaboration and planning for access should be pursued in parallel in

order to maximise speed and impact. An analysis of the scientific, regulatory, economic, ethical, and societal factors that characterise other disease areas would support a critical discussion of the current status of R&D in Alzheimer's disease and other dementias.

Supporting Research and Innovation: Modern science has only cured about a dozen diseases, and only through extended periods of incremental innovation. The traditional, linear model of innovation is being replaced by more flexible, responsive and open approaches. Cross-sectoral collaboration and interdisciplinary research has the potential to advance our understanding of how Alzheimer's disease develops and to translate emerging knowledge more efficiently into preventive and therapeutic approaches. Governments will need to invest immediately to drive comprehensive efforts in basic and applied science in order to better understand the complex pathologies of dementia. Clinicians need to engage with, support and understand the next generation of Alzheimer's medications. payers will need to understand the value of potential treatments, moving from an observational role to active support for innovation. Businesses will need to be transparent about the cost of the therapies they are offering and to be realistic as regards the price. The whole concerned community needs to come together to develop short- and long-term plans that will enable: 1) continuous progress in basic science; 2) to translate patient preferences into mutually accepted outcome measures; and, 3) to bring innovations to markets.

Effective engagement of those with Alzheimer's and their caregivers: A better understanding of the needs and desires of people living with dementia is essential to inform policy development, regulatory and access frameworks, the design of efficient clinical trial strategies and building of the readiness of health systems for near-term therapeutic innovations. A system to capture quality real world evidence about the clinical effect of Alzheimer's disease interventions in heterogeneous populations is needed to assure continuous and rapid innovation. Researcher engagement with patients, caregivers and advocacy groups to collect patient-related outcome measures can be employed to increase the success of clinical trials, to enable a proactive discussion with regulatory agencies, to help the definition of therapeutic value, and to ensure that future therapies address patients' needs.

A continuum of collaboration: No single stakeholder or sector alone can address the complex pathological processes that lead to Alzheimer's disease dementia or the organizational innovation needed to foster a comprehensive intervention strategy. Partnerships enable a leveraging of individual strengths to generate greater value than the sum of what each partner alone could accomplish. Strengthening values of open science amongst stakeholders would (1) improve the efficiency of R&D through a faster implementation of emerging technologies; (2) increase investment/reduce cost; (3) foster knowledge spill overs for a faster dissemination of results between academia and firms; (4) support linkages between national dementia plans and global strategies; and (5) help to meet information needs of policy makers.

Realigning investment, incentives, and research priorities: Policy makers, patient-focused advocates and public funders are at the forefront in linking research, drug development, access and patient engagement where traditional incentives (e.g. financial return, intellectual property rights, scientific recognition) are inadequate. Scientifically sound data about the biological underpinnings of Alzheimer's disease are a key driver of stakeholder engagement, product development and regulatory decision making. Public funders aim to advance therapeutic and diagnostic innovation via a strengthening of fundamental and translational research; supporting standardisation; avoiding over-claiming the significance of research findings; supporting the publication of negative research results; and helping knowledge sharing across disciplines and therapeutic areas. Patient advocacy and other

civil society groups are critical drivers of bringing patient perspectives to bear and driving collaboration and overall progress.

Defining therapeutic value: Coverage and payment decisions for any future diagnostic and therapy for Alzheimer's disease and other dementias should be based on available medical evidence of positive health outcomes and relative costs of existing therapies. Policies also need to consider the ethical, epidemiological, and economic opportunities and constraints of a possible future disease-modifying treatments. In order to develop the adequate reimbursement schemes for Alzheimer's it is important to understand the immediate and long-term economic and social impacts on families and countries, i.e. health care expenditures, GDPs, job markets, and health disparities. Resources to be allocated to reimbursement must be decided in view of the relative priority of various diseases competing for government and social security funding, of which Alzheimer is one only. Policy questions that need to be addressed are, for example: Do we need a new patient-centric value framework that includes all impacts on patients, caregivers and society – including quality of life? How to adequately capture long-term benefits and costs of disease and therapy from a dynamic and innovation-friendly reimbursement policy? What are the options for a sustainable reimbursement scheme for Alzheimer's disease? Pricing needs to be transparent, and to reflect the actual cost of innovations.

Planning for access: The rising prevalence of people living with dementia will generate further fiscal and social pressures that require additional incentives and reform approaches both in the private research industry, governments and the civil society. However, the traditional health insurance system may not offer the right tools to counter the dementia challenge. There is an urgent need for all stakeholders to develop evidence-based and cost-effective solutions in order to prepare health care systems to provide optimal care of dementia patients, enable early diagnosis and deliver effective preventive and therapeutic measures. Policy makers have already introduced a number of institutional reforms in response to the financial and organisational pressures resulting from ageing populations, rising R&D costs, and other economic constraints.

Improving pathways to diagnosis and treatment: Currently, health care providers' limited understanding of Alzheimer's disease and treatment options fosters a passive approach to the disease in the medical community. Combined with social stigmas, this approach often leads to extensive delays in the diagnosis of Alzheimer's disease, and subsequent discussion of options with patients. However, opening and improving theses diagnostic and treatment pathways will become increasingly important as new and earlier disease modifying therapies are developed. A variety of stakeholders, including patient organizations and health care providers, must work to enhance understanding of Alzheimer's disease generally, as well as current and possible future treatment options. Such measures will be critical to ensuring that future therapies reach patients at the stage of disease progression when treatment can be most impactful.

Enabling timely detection: Currently, the limited availability and clinical use of diagnostic tools and services, including both cognitive and biomarker-based approaches, hampers the development of effective therapies, and undermines long-term public health outcomes. There is a need to translate emerging tools for early diagnosis into clinical practice; this requires close collaboration between innovators, policymakers and the payer community. Significant progress in biomarker validation and qualification will only be possible with a more in-depth understanding of the relevant molecular and biochemical underpinnings of Alzheimer's disease.

INTRODUCTION

The growing proportion of older people – both in terms of absolute numbers and as a total of the population – is leading to a drastic increase in dementia's already significant, worldwide burden. There is unequivocal evidence about the enormous impact of Alzheimer's disease on individuals, cares, health systems and economies. The societal and economic challenges of Alzheimer's disease and other dementias require immediate and scaled action across sectors and societies.

Active engagement of public and private stakeholders is needed to achieve the global goal to prevent and effectively treat Alzheimer's disease by 2025. However, the path forward will depend on the provision of adequate resources, scientific progress, and information sharing across sectors and partners. In this context the second Lausanne Workshop (15-16 December 2015, Lausanne, Switzerland): 'Global Action to Drive Innovation in Alzheimer's disease and other Dementias – Connecting Research, Regulation and Access') convened stakeholders engaged in research and health innovation for Alzheimer's disease and other dementias. Government officials, representatives from academia, industry, and civil society organisations jointly discussed approaches to encourage more innovative research, shared governance, and implications in access and rational use of future Alzheimer's diagnostics and therapies.

Healthy ageing and dementia have rightly become key policy priorities for countries across the world for reasons including economic productivity, financial stability and sustainability, social engagement, human rights and ethics (OECD, 2011). Human life span and age-related diseases continue to increase, leading to rising concern about the ability to provide sustainable research and public-health systems. The current innovation model in biomedical research and drug development has been proven to be inadequate in Alzheimer's disease and other dementias – high investment risks and limited success of clinical development programmes have pressured stakeholders to establish a relationship of trust, collaboration and information sharing. Dementia has been the focus of increased international discussion, starting with the G8 Dementia Summit (London, 2013), which led to the establishment of the World Dementia Council, and continuing with subsequent legacy events hosted by other G7 countries and many others.

The first Lausanne Workshop "Enhancing Translational Research and Clinical Development in Alzheimer's Disease and other Dementias: The Way Forward" in Lausanne, Switzerland (11-12 November 2014), maintained the growing momentum in order to discuss options to drive forward a change in the global paradigm in biomedical research and health innovation for Alzheimer's disease and other dementias. The workshop demonstrated that therapeutic research needs to shift from diagnosed dementia to pre-clinical stages, which will require more sensitive diagnostic tools, new trial designs, and more flexible regulatory processes. Key messages and policy recommendations of the first Lausanne Workshop have been included in OECD reports (OECD, 2015a; OECD, 2015b). The reports simultaneously addresses all the pieces of the dementia puzzle – the still inadequate care for people living with dementia today; the gaps in research and in the balance of risk and rewards for dementia research; and the potential for bringing together genetic, environmental, personal and health system data to better understand this complex disease.

Box 1. Facts and figures: population ageing and dementia[ii]

- The world has added approximately one billion people in the span of the last twelve years and reached 7.3 billion in 2015. The world population is projected to increase by more than one billion people within the next 15 years, reaching 8.5 billion in 2030, and to increase further to 9.7 billion in 2050 and 11.2 billion by 2100.
- Globally, life expectancy at birth is projected to rise from 70 years in 2010-2015 to 77 years in 2045-2050 and to 83 years in 2095-2100.
- Population ageing results from a declining fertility rate and rising life expectancy: In 2015, there were 608 million people aged 65 or over, comprising 8.3% of the global population. Rapid ageing occurs in all parts of the world, for example (percent of population 65 or over in 2015/ 2050/ 2065): Africa (3.5%/ 5.9%/ 7.9%); Asia (7.5%/ 18.2%/ 22.3%); Europe (17.6%/ 27.6%/ 27.9%); Latin America and the Caribbean (7.6%/ 19.5%/ 25.0%); North America (14.9%/ 22.7%/ 24.3%); Oceania (11.9%/ 18.2%/ 20.2%).
- Dementia is one of the most frequently seen degenerative conditions in the older part of the population, with Alzheimer's disease being its most common form (50-70% of dementia cases). Since dementia is strongly associated with old age, increasing life expectancies across the world will mean more people living with the condition.
- In 2015 over 46 million people live with dementia worldwide; this number is estimated to increase to 131.5 million by 2050.
- The total worldwide societal cost of dementia in 2015 was USD 818 billion; estimated at 2 trillion dollar in 2030.

The first WHO Ministerial Conference on Global Action Dementia (Geneva, 2015) marked another stepping stone in our collective action to tackle dementia. In her opening remarks Dr. Margaret Chan, Director-General of the World Health Organization, stated that "Urgency inspires invention. The solutions being proposed are foresighted as well as innovative, as they can carve out ways of pushing other badly needed medical products through discovery and regulatory approval and onto the market. …The plan must be backed by strong political and government commitment expressed through resources and practical policies. Coping with dementia is also a health systems and social welfare issue." The conference concluded that a more coordinated, global response to the challenge of dementia, governments and other stakeholders should raise awareness about the role and responsibilities of major stakeholders in addressing the public health and socio-economic challenges of dementia. At the conference Marc Wortmann, Executive Director of Alzheimer's Disease International (ADI) and co-organiser of the Lausanne Workshop, said: "We need to increase efforts on research but also recognise the role of civil society organisations as key advocates for improvements in dementia care and policies. The only way forward is through co-ordinated global action". As a direct outcome of the event participants agreed on key principles to promote action on dementia and address the challenges posed by dementia and its impacts[iii].

The second Lausanne Workshop provided an international forum to articulate achievements and opportunities in biomedical research and health innovation for Alzheimer's disease and other dementias – aiming to address the challenges and barriers to the introduction into the market of effective treatments and diagnostics by 2025. The importance of this work was also emphasised by the "Programme of the Netherlands Presidency of the Council of the European Union".[iv] The Netherlands Presidency discussed options to accelerate the translation of research into innovative therapeutic and diagnostic options for patients at socially acceptable cost. Peter Schintlmeister, Chair of the OECD Working Party on Biotechnology, Nanotechnology and Converging Technology

referred to the new EU Clinical Trials Regulation[v]: "Though the new Clinical Trials Regulation shows legal force only in the EU it will eventually have a global impact. In Lausanne we discuss options to translate its key aims into practice for research and development in Alzheimer's disease: harmonised and simplified procedures, mutual understanding between jurisdictions, data transparency, flexibility and efficiency of clinical trials". Efforts such as IMI's European Prevention of Alzheimer's Dementia (EPAD) and the Global Alzheimer's Platform (GAP) represent innovative approaches to the construction of a standing, global Alzheimer's clinical trial platform and to the reduction in the time, cost and risk of advancing innovative treatments to those with or at risk of Alzheimer's.

Box 2. Message by Hilary Doxford, Lausanne, 16 December 2015:

Living with Dementia

I like many are frequently guilty of forgetting the overall ambition of our work. It is not just about science, politics, policies and metrics because above all it is about life, a happy life to be lived as well as possible within those constraints that are beyond human control. In the dementia arena we are striving to bring more of those constraints under our control and as quickly as possible. It is easy to forget the human face of dementia and become embroiled in our own little micro-worlds. I cannot speak for people with dementia, only as a single person with a diagnosis of Alzheimer's. My words may resonate with some and be unrecognisable to others. But whichever, we must not allow ourselves to be distracted from our prime purpose. We all have a part to play, including people with dementia and I hope to overcome perceptions that we are unable to contribute; many of us can add value. Don't assume we can't, presume we can.

I hoped to let attendees know how much their efforts are appreciated, but also to remind them that they must always retain and involve the human face of dementia in all they do and to put this to the fore. Remembering the sadness dementia causes motivates me to do all I can whilst I can. It is important to push boundaries and disrupt conventional thoughts and practices. We must all work as a team and I include those with a diagnosis of dementia. It no longer surprises me how many professionals overlook the abilities of people with dementia or because we can still contribute are told we can't have dementia. Likewise I find it upsetting when those with dementia unfairly criticise those who try to help us.

At the end of the day, I cannot convey all the above, so by giving an insight to myself and my life I hope I will have shown my appreciation for all that is being done and to act as a little nudge to keep working as hard as possible to achieve our dream. My enemies are time and fear. But my joy is the number of friends I have as I consider everyone trying to help me a friend and because of my friends I have great hope that my life will stay under my control.

This report brings together the policy issues around the question of what can be done to strengthen research, regulation and access to innovative diagnostics and therapies for Alzheimer's disease and other dementias by 2025. At the event participants identified a number of options in order to enhance collaborative action to put in place the necessary strategies, policies and resources. The success of the Lausanne Workshop and ensuing Lausanne Dialogue can be measured in how stakeholders engage in an ongoing dialogue and concrete actions towards the goal to prevent and effectively treat Alzheimer's disease by 2025.

STRENGTHENING INNOVATIVE RESEARCH AND DRUG DEVELOPMENT

Box 3. Key messages: strengthening research and development

- Open and collaborative research across medical scientific disciplines has been proven to be an effective tool to advance our understanding of how Alzheimer's disease develops and to translate emerging knowledge into innovative therapeutic approaches.
- Because time cycles of biomedical and technological innovation are slow, our current research and development infrastructure often is sluggish and inefficient. We need to learn (faster) from failures in clinical trials, implement feed-back mechanism into R&D processes, thereby reducing recruitment delays and the attrition rates in clinical trials, and increase the efficiency in therapeutic development for Alzheimer's disease and other dementias.
- The inadequate understanding of the fundamental processes leading to Alzheimer's dementia represents a major obstacle for innovators; large investments in clinical research should be balanced with funding of upstream biomedical research.
- Future therapies for Alzheimer's disease could be a combination of symptomatic drugs with a rather short-term impact, and disease modifying therapies that slow cognitive decline over the long term.
- There is a need to integrate biomarker research into medicine – expanding the use of biomarkers beyond clinical trials, to become important tools for regulatory decision-making and commercial diagnostics. An important goal in biomarkers research is to identify class-specific markers that could increase the efficiency of diagnosis and drug testing. In order to clinically operationalise biomarkers we need to strengthen academic-industry partnerships for co-development of drugs and biomarkers.
- Due to the paradigm shift that prioritizes studying patients earlier in the course of disease progression, it has become even more important to understand the needs and desires of people at risk of dementia. Researchers and regulators must work together in order to translate patient preferences into mutually accepted outcome measures.
- Alzheimer's is a progressive and, to date, inevitably fatal disease; at some point regulators, patient communities and innovators need to discuss what might be an acceptable side-effect burden of a potential therapy. However, it is not clear whether stakeholders are ready to accept higher efficacy at the cost of tolerability, such as in cancer treatment.

Drug development for Alzheimer's disease remains a high risk endeavour. Despite the significant medical and scientific advances in recent decades, most research and development programmes on potential drugs for Alzheimer's have been unsuccessful – there are no approved treatments to prevent, slow down or cure Alzheimer's disease. Challenges arise in the understanding of the disease, the diversification of potential targets for drug development, the establishment of validated biomarkers, and the translation of research findings into clinical applications (Gauthier, Albert, Fox et al., 2016). Additional ethical and legal challenges confronting researchers and regulators are arising as a result of the conduct of clinical trials involving pre-symptomatic and early stage people living with dementia.

In taking advantage of the growing evidence base in molecular biology, researchers are re-evaluating the existing disease paradigms and are setting-up alternative concepts of Alzheimer's disease that combine biological and clinical features from all disease stages. These changes require new and standardised disease models, adequate diagnostic tools, flexible trial designs, and more

aligned regulatory processes to monitor disease progression and to evaluate therapeutic efficacy. This section aims to discuss the novel diagnostic and therapeutic approaches that are currently in development. How to link patient preferences with mutually accepted outcome measures and related therapies?

"In order to achieve our goal to deliver a disease modifying drug by 2025 we need to: act together now and accelerate innovation; set ambitious mid-term objectives for advancing therapies and diagnostics; and simultaneously plan for future access." (George Vradenburg)

Box 4. Summary of Keynote Speech given by Dr. John C. Reed

Dr. John C. Reed (Global Head of Pharma Research and Early Development at Roche) provided the researcher's perspective on the development of disease-modifying treatments for Alzheimer's disease. A fundamental challenge in Alzheimer's disease, which represents the most significant threat to global public health in the 21st Century, is the biological complexity of the disease. The good news is that our scientific understanding is progressing and the current clinical trial pipeline for Alzheimer's disease has molecules targeting a number of pathways potentially important in the development and progression of the disease. As our understanding increases it has become clear that the onset of Alzheimer's disease occurs many years, perhaps decades, before symptoms are recognised. Moreover, recent clinical trials have shown large variation in the rate at which people progress to Alzheimer's disease. If we are to modify the course of the disease we need to be able to diagnose people in the early stages of Alzheimer's disease, and identify those whose disease will progress quickly. More effective early identification and diagnosis are critical for recruiting volunteers to clinical trials if we are to demonstrate the potential disease-modifying benefit of novel treatments.

Having selected the right trial population, determining relevant and reproducible outcome measures in the absence of biomarkers remains an issue. Current outcome measures were developed to assess symptomatic benefit of interventions and, while improving symptoms is important, changing the course of Alzheimer's disease must be our goal. It may take many years to reliably evaluate whether this has been achieved, beyond the scope of most clinical trial timelines. It is likely that any improvement in clinical outcome will be modest and improvements in treatment will be incremental (as seen in other diseases, such as cancer). How, then, would we value the benefit of a disease modifying treatment for Alzheimer's disease?

Given the huge personal impact, for the individual and their family, and the enormous societal costs that result from a diagnosis of Alzheimer's disease, we urgently need to examine the balance of economic burden, social care costs and medical costs through a new lens. We all need to work together to reassess the way in which we encourage, support and measure innovation and to make change happen for the benefit of those living with Alzheimer's disease and their families, now and in the future. The Lausanne Dialogue is a critical step towards making this happen.

Key challenges need to be addressed in order to accelerate innovative research and development of effective diagnostics and therapies. It is key to improve our understanding of the foundational science of Alzheimer's disease and other dementias by strengthening basic research, so that investment in clinical trials can be targeted more effectively. There is a need for further investment into upstream research to help understanding the symptoms and causes of dementia.

The Integrated Development Initiative was presented by Raj Long (R. Long). It follows the UK G8 Summit on Dementia, December 2013 and aims to assess the possible collaborative efforts amongst regulators in order to develop a more conducive environment to facilitate successful dementia drug development. At the 1st Global Dementia Regulators Workshop (10 November 2014, Geneva) representatives from 10 regulatory agencies including the US, EU, Canada, Japan, Switzerland, Germany, Italy, Denmark, and the Netherlands identified six work areas and a 2nd convening in June 2015 hosted by the Italian regulator AIFA in Rome:

- **Attrition Analysis**, led by the Imperial College and UK DoH: Analysis of past pipeline for dementia treatments, exploring possible reasons for failures of dementia programmes.

- **Clinical Trial Efficiency**, led by SwissMedic: This work will analyse (retrospectively) features and commonalities of failed studies relative to Scientific Advice obtained (design, endpoints etc.) with the goal of sharing learnings.

- **Composite End Points**, let by The Federal Institute for Drugs and Medical Devices (BfArM) Germany: Activities aim to improve standardisation and validation of cognitive endpoints, focusing on quantifying cognitive impairment in the earlier stages of dementia.

- **Risk/Benefit Ratio**, led by the Danish Health and Medicines Authority (DKMA): This work considers the balance of benefits, risks and uncertainties for eventual promising medicines for Alzheimer's disease and how to manage this balance from a licensing perspective. Issues considered include, for example, assessment of whether existing regulatory frameworks allow sufficient flexibility while still ensuring that inefficacious and/or dangerous medicines are not granted a license or are taken off the market as soon as possible.

- **Modelling and Simulation**, led by The Italian Medicines Agency (AIFA): Work includes the evaluation of the appropriateness of modelling and extrapolation to bridge gaps in science.

- **Multilateral Collaboration**, led by the European Medicines Agency (EMA): This work package aims to promote global regulatory efficiency and consistency. A sub-group of PMDA, Health Canada, EMA and FDA has been established in order to perform a comparative review of the FDA and EMA guidelines on dementia, focusing on main issues of relevance to, and from the perspective of global development.

In addition to the work on Integrated Development R. Long published an independent report titled "Finding the Path for a Cure for Dementia". The report outlines four 'actions for change' steps R. Long has highlighted as key steps in order to find a cure for dementia:

- **Action 1**: Use the learnings from the regulators to agree on principles for facilitating consistent global development pathways;

- **Action 2**: Understand and agree on the gaps in the basic science (both amyloid and non-amyloid approaches) and take action to address these;

- **Action 3**: Develop the International Dementia Advisory Platform (IDAP);

- **Action 4**: Support the assessment of the necessary clinical evidence required in dementia development programmes for regulatory assessment.

"This is what caused a movement in HIV 30 years ago: prioritisation, funding, innovative management, collaboration and access. We need to take the bull by the horns and seek political endorsement." (Dr. R. Long)

Initial results from the attrition analysis and work on clinical trial efficiency show that often failures were driven by pursuing development programmes based on inadequate trial results – translational inter-confirmatory was often not met. In order to increase the efficiency of clinical programmes and identify failures earlier, we need to agree on and apply stringent criteria at the transition of each phase.

The coordinative work on the Integrated Development Initiative recommendations will now be taken on by the OECD for supporting the regulators network and Alzheimer's UK (ARUK) for

leading the IDAP and research framework. The OECD and ARUK are both well placed because of their global outreach and scientific expertise respectively.

Dr. Maria Isaac elaborated on options to support the qualification of novel methodologies for regulatory use at the European Medicines Agency (EMA). The creation of a development road map for innovative products for Alzheimer's disease involves two parallel work streams: scientific advice and qualification advice. Scientific advice is product and indication specific and delivered in 40-70 days. Qualification of Novel Methodologies is broader in scope allowing rapid update of translational pharmaceutical science for a global medicines development. Note: The term, 'qualification,' means the official regulatory opinion on the specific use of the proposed method (e.g. use of a biomarker) in a R&D and/ or clinical context after the review of the presented data. It can be a way of streamlining the marketing authorisation procedure.

Regulators base decisions primarily on risk/ benefit analysis. In Alzheimer's disease, for example, the measurement of clinically meaningful benefit has proved challenging. Sensitivity of measurement of clinically meaningful benefit can be improved by the use of biomarkers to choose the right population to be treated at the different stages of the disease. It is all about treating the right patient at the right time.

Early engagement with the agency during the planning stage of the projects has been key in building a regulatory framework to support future development of candidate therapies for Alzheimer's disease. Thanks to the advances in translational science we can start to discuss combination treatments to treat different stages of Alzheimer's disease at different stages.

There is general agreement that developing effective prevention strategies for Alzheimer's disease and other dementias is critical to diminishing the burden on societies and economies. Often dementia prevention is divided into three categories (Rubinstein et al., 2015): primary prevention, reducing the prevalence of disease by eliminating or treating specific risk factors that may decrease or delay dementia onset; secondary prevention, reducing the prevalence of disease by shortening its duration; tertiary prevention, reducing the impact of complications of long-term disease and disability. Despite the low success rate of clinical programmes in Alzheimer's disease, stakeholders remain confident in the goal of developing effective preventive measures and disease-modifying therapies for Alzheimer's disease and other dementias (Cavedo, Lista, Khachaturian, 2014). Given the long development timelines of therapeutic innovation prevention of Alzheimer's disease and related risk reduction may be the most effective approach to delay onset of dementia, and potentially reduce the number of new cases.

As laid out by Prof. Dr. Tobias Hartmann, the key components of Alzheimer's risk reduction strategies are nutrition, physical activity, cognitive training, social engagement, optimised medication, and the management of other medical risk factors (e.g. cardiovascular disease, diabetes) – often referred to as multi-domain intervention. Our current understanding is that we need to act early, before full symptomatic presentation of dementia; implement several pharmacological and non-pharmacologic options in order to manage concomitant medical risks; and harness a wide array of non-pharmacological interventions. As the project coordinator of the EU funded LIPIDIDIET project,[vi] Prof. Dr. Tobias Hartmann explained that the combination of a multi-nutritional diet with current medical therapies could slow the onset and reduce the progression of symptoms of Alzheimer's disease. As such, the principal aim of current intervention strategies in Alzheimer's disease is to combine medical with nutritional options as both primary and secondary prevention.

Initial results show that a multi-domain intervention can increase cognitive performance (Nagandu et al., 2015). However, Dr. Hartmann noted that, to date, there is insufficient evidence that we can achieve effective prevention of Alzheimer's disease through dietary, lifestyle and pharmacologic intervention alone. Researchers have called on the WHO and the World Dementia Council to strengthen investment and collaboration across national governments and funding bodies in order to deliver population-oriented clinical trials that monitor and assess risks in relation to lifestyles and diets (Orrell and Brayne, 2015).

Dr. Claus Bolte discussed operational and methodological issues that lead to the discontinuation of a large number of clinical studies in Alzheimer's disease. For "clinical trial efficiency", he suggested operationalising a retrospective, as well as prospective, project: the retrospective project would first seek to understand commonalities and features of failed studies relative to the scientific advice provided. Neither the molecule tested nor data generated would be (re-)investigated, but rather the idea is to learn from failed studies with a focus on study/ programme design, endpoints, population, disease stage, dose-selection, and regional recruitment issues with inclusion/ exclusion criteria, etc. Highly specialised regulatory review units ought to look beyond dementia or confined therapeutic areas to gain insight from innovative drug development programs in oncology (master protocols, platform trials) and anti-infective compounds with designated pathways. Subsequently, the prospective project would take these key learnings on board to define and implement an operating mode for synchronizing scientific advice in Alzheimer's disease amongst major agencies. A longer-term vision would be a coordinated consultation process to provide joint scientific advice to commercial sponsors of Alzheimer's disease for the design of clinical trials and development programmes, thereby avoiding an unnecessary duplication of efforts when dealing with different regulatory authorities worldwide. Ideally, this should be combined with HTA advice to expedite market access and reimbursement when applicable.

"It seems there are difficult translational gaps between an early proof-of-concept and the selection of endpoints for different (sub-)populations. Maybe we don't have as many unsuitable molecules as we previously thought, but they just weren't developed appropriately; potentially also with conflicting scientific advice. Nobody is to blame, but we should all be learning. Lausanne provides an excellent opportunity for this."(Dr. Claus Bolte)

As an example of how regulatory agencies are taking ownership of the growing dementia issue, Dr. Yoshiko Komuro presented key processes at the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) and at the Ministry of Health and Labour Welfare (MHLW):

- The "Human Resource Exchange Programme" between the PMDA and academia (University of Tokyo Hospital, Tokyo) aims to strengthen regulatory science, to use state of the art technologies, and to implement regulatory strategies in upstream research. Ultimately, the programme should help both increase the efficiency of translational research and PMDA services;

- The "Regulatory Science Research Project" is another activity between the PMDA and the University of Tokyo Hospital, Tokyo. It aims to promote the establishment of guidelines for development/ clinical evaluation of innovative drugs for Alzheimer's disease[vii];

- "Pharmaceutical Affairs Consultation" on R&D Strategy is a new consultation framework in which the PMDA provides guidance to academia and venture businesses that have promising candidates for innovative medicines. The advice includes quality criteria, pre-clinical and early stage clinical studies, and regulatory requirements on pivotal trial design.

- The SAKIGAKE package strategy was launched by MHLW in 2014 to lead the world in the practical application of regulatory advice for innovative medical products. In case of SAKIGAKE designated item, various advantages are available, for example, substantial pre-application consultation (de facto review before application) and prioritized review.

- By utilizing this scheme effectively, it is expected that innovative drugs for dementia will be available in near future. PMDA/MHLW is happy to collaborate with other regulatory agencies, academia and industry to promote anti-Alzheimer's disease drug development.

Ultimately, the safety and well-being of volunteers in clinical trials are corner stones of drug development programmes. Informed decision making by volunteers in clinical trials and data privacy remain at the centre of any research activity involving human subjects. Special attention needs be paid to the ethical issues involved when dealing with the inclusion in clinical trials of patients in very early disease stages or healthy patients with a genetic predisposition for Alzheimer's disease. It is also critical to ensure that patient organisations play an important role in collaborative research partnerships as they help ensure that patients' needs are taken into consideration.

Prof. Dr. Andrea Pfeifer summarised future therapeutic strategies for Alzheimer's disease:

- **Consensus on the evolution of pathology in Alzheimer's disease**: Evidence from many independent research centres strongly support the existence of a specific Alzheimer's disease, as defined by the presence of amyloid beta plaques and neurofibrillary tangles. As cognitive performance declines from Preclinical and Prodromal stages to Alzheimer's dementia, three declared pathologies are involved: amyloid beta plaques, neurofibrillary tangles and inflammation. Although amyloid beta plaques may play a key role in Alzheimer's disease pathogenesis, the severity of cognitive impairment correlates best with the burden of neocortical neurofibrillary tangles.

- **Current focus of therapeutic research**: There are two main approaches currently being pursued by the industry – symptomatic and disease modifying. The latter has two targets, namely, amyloid beta and neurofibrillary tangles. The pipeline consists of four candidates (in Phase 3) for symptomatic treatment, eight candidates (Phase 2, Phase 3) in disease modifying targeting amyloid beta, and three candidates (in Phase 1b and Phase 3) in disease modifying neurofibrillary tangles.

- **Emerging strategies and recommendations**: Targeted permutations of combination therapy are envisaged in the following order – the best scenario is disease modifying combination therapy followed by disease modifying monotherapy and then symptomatic combination therapy and lastly symptomatic treatment. The stretched target and the best of all is prevention therapy for which diagnosis is critical and needs to be developed on an urgent basis.

- **Regulation**: On the regulatory front there is need for early dialogue between agencies and industry, a systems to support development and implementation of surrogate markers in clinical trials, approval of drugs based on targeting validated risk factors, accelerated development of combination therapy through regulatory acceptance of appropriate preclinical and clinical safety data, and allowing early access to new medicines with highly positive Phase 2 and Phase 3 results through conditional approval / Breakthrough Designations / Treatment IND.

- **Collaboration**: A multi-stakeholder platform is needed to foster interactions between patients, scientists, regulators, payers, and government. There should be a global effort to

take a holistic treatment and prevention approach, including drugs, food and physical activity.

"Significant advances in science can help target and pipeline diversification. The Dementia Discovery Fund is a unique collaboration between governments, NGOs and industry to drive research on targets that are not in the mainstream. This I would call an important achievement since the first Lausanne Workshop last year. Furthermore the implementation of new trial platforms is becoming a reality with IMI-EPAD poised to enrol its first cohort study participant in April 2016." (Dr. Luc Truyen)

Linking biomarker research with regulatory science and access to markets

Advances in the understanding of the progression of dementia at the cellular and molecular levels have spurred new research approaches. New technologies will facilitate diagnosis of the disease and development of drugs for dementia. As the relationship between a class of drugs and a biomarker becomes better understood, there is hope that it will be possible to identify the patients most likely to benefit from the drug at increasingly earlier stages of the disease. Early and frequent interaction between industry and regulatory bodies will ensure studies are appropriately designed and biomarker test performance is well characterised.

"The need for early detection and treatment, while a hot topic in clinical research, has not yet translated into a change in clinical practice, or into payer and policy maker actions. As a result, the patient journey remains unnecessarily long and arduous. In clinical practice, diagnosis occurs late if it happens at all." (Phyllis Barkman Ferrell)

Only when cognitive and functional deficits significantly impact everyday life are patients and caregivers prompted to seek healthcare consultation. The lack of consensus on the appropriate tools to detect/ diagnose the disease, and the limited availability of treatments, often hinders engagement, detection, and diagnosis by the physician and fosters a wait and see approach. Unfortunately, the result of these delays may be that neurological decline progresses to a stage where there is little or no benefit from a potential next generation disease modifying therapy.

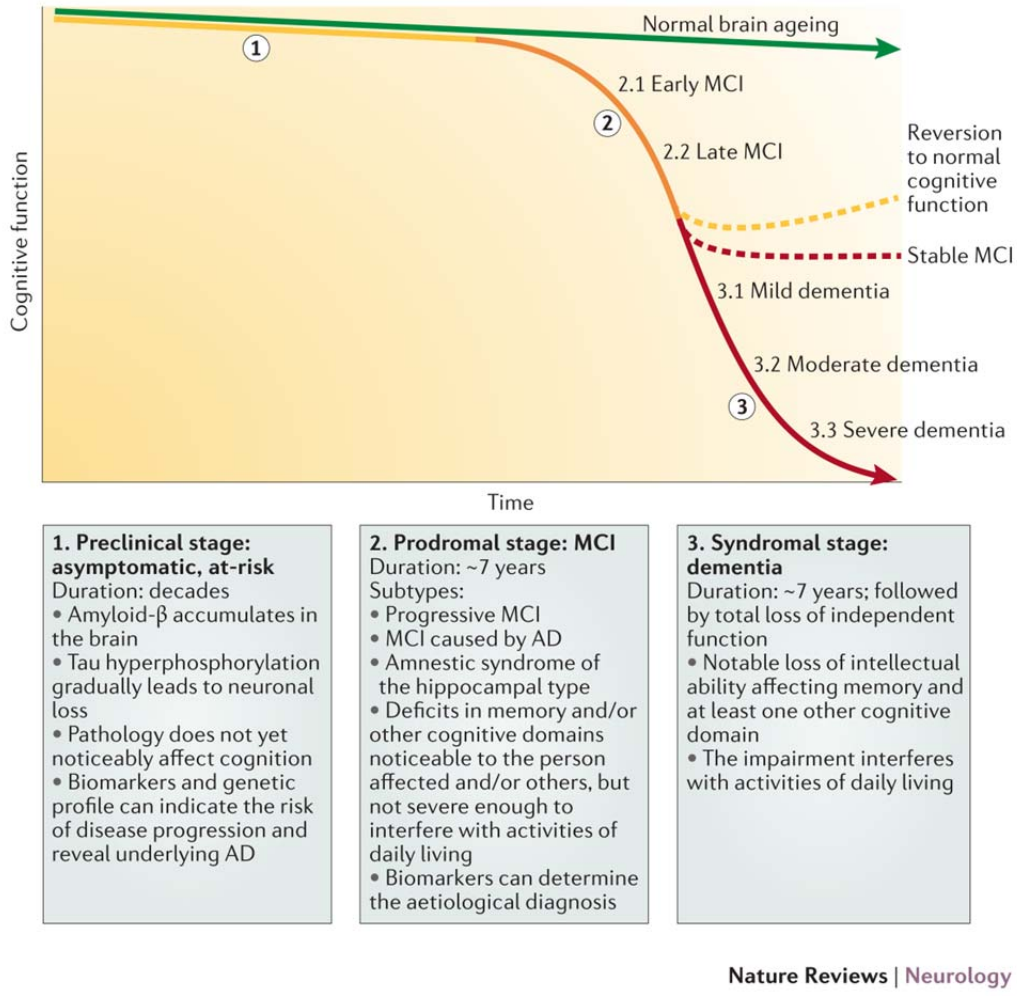
Dr. Husseini K Manji elaborated on how biomarkers are used in Alzheimer's research, development and diagnosis with the ultimate goal to improve patient outcomes and care. However, as Dr. Manji and Dr. Bolte pointed out, we need to clearly distinguish between the various contexts of use and application areas of biomarkers. Currently we are looking at:

- Prognostic markers to categorise patients by degree of risk for disease occurrence or progression;
- Predictive markers to categorise patients by their likelihood to respond to a particular treatment or to experience adverse events;
- Pharmacodynamic markers that show that an expected biological response has occurred in a patient after receiving a pharmacologic intervention;
- Disease progression markers to detect treatment-related changes in disease pathophysiology; and,
- Surrogate markers to predict clinical benefit or harm or lack of benefit or harm.

"A key question is how can we use the potential of biomarkers to move from (patient) group differences in clinical development to individual differences in, for example, precision medicine." (Dr. Husseini K Manji)

In his presentation Prof. Dr. Hampel pointed out the critical role of biomarkers in pharmaceutical research and drug development for Alzheimer's disease. Biochemical, genetic, electrophysiological, and neuroimaging markers form the basis of current research strategies in genomics and personalised medicine. In Alzheimer's disease and other neurodegenerative diseases and dementia disorders, biomarkers are needed to better understand the sequential and interacting pathological cascades; to identify individuals who are most likely to respond to a specific treatment in order to better 'enrich' the targeted subject population of clinical trials; and to assess the safety and effectiveness (outcome) of potential therapies (Dubois et al. 2016; Hampel et al., 2010). Validated and qualified biomarkers help the refinement and harmonisation of criteria of Alzheimer's disease across all stages in order to ensure a better definition of patient populations in clinical trials. A precise and differentiated biological staging system has yet to be definitely established (see Figure 1; Hampel and Lista, 2016).

Figure 1. Hypothetical staging model of sporadic Alzheimer's disease. Published, Nature Reviews Neurology (Hampel and Lista, 2016).



The question remains to be answered as to when Alzheimer's disease starts and what are the dynamic processes and factors that turn the 'normal' ageing process into a biological and subsequently clinical disease? (Prof. Dr. Harald Hampel)

The positive impact of validating multi-modal biomarkers and imaging technologies on the acceleration of drug development processes cannot be overestimated. Clinical programmes in Alzheimer's disease and other relevant neurodegenerative and central nervous systems diseases take longer, are riskier and have lower regulatory success rates than in other indications – leading to very high development costs, attrition in subject compliance during lengthy studies, and limited therapeutic target diversity (Cummings, Morstorf and Zhong, 2014; Geoffroy, 2013). The qualification and validation of comprehensive exploratory and candidate biomarkers in Alzheimer's disease is a key driver of current research programmes in academia and the pharmaceutical industry, essential to accelerate the development of innovative diagnostics and therapies. However, despite major advances in biomarker validation and partial success in qualification, we still lack the means to identify all relevant molecular mechanisms or signalling pathways that could serve as biomarkers for the development and progression of Alzheimer's disease. The development of companion diagnostics would be a significant, but not complete, step towards our goal to understand, diagnose and treat Alzheimer's disease by 2025.

Given the substantial investment in clinical development programmes, increasing health care costs and loss of productivity due to Alzheimer's disease, biomarkers can have a substantial positive impact on future research and therapeutic costs. Technological innovation in identifying low-cost, non-invasive markers will also help to further reduce the current costs of approximately EUR 15.000 for a baseline set of biomarkers for Alzheimer's disease.

We need to strengthen collaboration and pool registries, cohorts, big and deep data and resources in 'think-tanks' to increase investment, share information, avoid redundancy and speed up the regulatory process at the interface between governments and industry.

"Cure never really happened in HIV, but, if adequately treated, became an asymptomatic disease. Therefore I wonder if we should set goal to make Alzheimer's an asymptomatic disease in people living with prodromal and pre-symptomatic Alzheimer's and to stabilise disease progression in patients with mild and moderate Alzheimer's disease." (Dominic Paes, Biogen International).

"For me the development of reliable biomarkers and diagnostic means to allow accurate staging of people with or at risk of Alzheimer's disease is a key goal of our current research."(Prof. Dr. Andrea Pfeifer).

The role of biomarkers in prevention studies aimed at delaying or preventing symptomatic progression in persons with Alzheimer's disease has been addressed by Dr. Serge Gauthier. Alzheimer's disease prevention studies take advantage of the knowledge gained from observational studies such as the Alzheimer Disease Neuroimaging Initiative (ADNI)[viii]: amyloid build-up precedes cognitive decline by many decades, allowing for primary prevention studies in higher risk populations defined by positive amyloid positron emission tomography (PET) scans. This build-up correlates to some degree with the apoE4 genotype, another biological marker for risk of Alzheimer's disease that is being used as inclusion criteria in prevention studies. Biomarkers of disease progression such as brain atrophy using magnetic resonance imaging (MRI), regional hypometabolism using PET with 18F-glucose, or elevation of levels of tau in cerebrospinal fluid (CSF) can be used as efficacy variables in prevention studies, particularly in proof-of-concept or as evidence for target engagement in Phase II studies, such as done by the Dominantly Inherited Alzheimer Network – Treatment Unit (DIAN-TU).

Prevention studies using biomarkers as entry criteria and/or as efficacy variables do have limitations such as the costs of screening for suitable candidates, relative invasiveness of the procedures (PET and lumbar punctures), access to the technology (PET, 3T MRI), and the potential lack of utility in the most common late onset dementias with multiple co-morbidities. Thus non-pharmacologic randomised clinical trials in ageing populations not pre-defined by biomarkers but rather by subjective cognitive complaints and/ or by clinical frailty are equally important, as demonstrated by the impact of the FINGER and the MAPT studies.

New cohort studies such as the Canadian Consortium for Neurodegeneration in Aging (CCNA) will allow for speedy recruitment for populations already deeply phenotyped at different stages of Alzheimer's disease (asymptomatic at low or high risk, mild cognitive impairment, mild dementia) and related conditions. The CCNA is one of a number of national, study-based or site-based registries of persons interested in volunteering for current and future prevention studies. The engagement of persons at risk of dementia in late life and of patients with symptoms, in addition to asymptomatic populations, is encouraged by patient-oriented associations such as Alzheimer Disease International (ADI). There is hope in early 2016 for improvement in trial designs and outcomes in both, prevention and treatment studies with the implication of all stake holders.

Engaging the patient community in developing real-world evidence

Box 5. Key messages: patient engagement

- Multi-disciplinary and cross-organisational collaboration can provide governments and researchers with the required real-world information for evidence-based policies and efficient research programmes.
- Many stakeholders still work in silos. We need to implement links between communities and efforts in both upstream research and clinical development in order to deliver processes that are more inclusive, transparent, and accountable.
- Science is moving fast, but access policies and health care systems readiness lag behind: early diagnosis and deeply-phenotyped patient registries can reduce the costs and delays of clinical trials and would accelerate the development of diagnostics and medicines for Alzheimer's disease.
- The engagement of the WHO is critical in order to make Alzheimer's disease and other dementias a global health priority, to achieve our goals, and to improve diagnosis, treatment and care of all patients in both resource-limited and industrialised countries. A formal resolution on dementia as a threat to healthy ageing by the World Health Assembly (WHA) would be a significant step forward.
- Stakeholders need to move from anecdotal speaking roles to widespread, symptomatic and active engagement of people living with dementia and care givers. Their moral force and knowledge is the driving force of our efforts.

The second Lausanne Workshop aimed to steer a multi-stakeholder discussion about future options to manage access, costs and return of investment of future diagnostics and therapies for Alzheimer's disease and other dementias. The treatment of Alzheimer's disease and its symptoms remains very challenging, given the meagre overall apparent benefit of existing treatment strategies. While some may describe the therapeutic horizon as promising, such characterisations inherently acknowledge that the future is uncertain and remains unproven. The social and economic challenges of Alzheimer's disease are significant for patients and will inevitably lead to very large downstream burdens for their families and society.

"We must link our actions to our goal and hold ourselves accountable. This can drive the delivery of next generation symptomatic treatments and a cure for Alzheimer's disease by 2025." (George Vradenburg)

In response to the multifactorial nature of Alzheimer's pathologies and due to high resource needs, collaborations across scientific disciplines and institutions have been evolving. Stakeholders in academia, small and medium-sized biotechnology companies and the pharmaceutical industry are in a position to make Alzheimer's and other dementias a priority area leveraged through closer, pre-competitive and cross-sector collaborations. Governments and patient advocates play a leading role in strategic partnerships to drive joint thinking and action across sectors to solve challenges, advance opportunities and reduce risk in research and health innovation. Early collaboration among the innovator, the regulator, and payer could accelerate the medical and scientific challenges in translating innovative research from the laboratory to the bed-side. Public-private partnerships and open source networks represent the most prominent examples of collaborations, serving as innovation platforms to overcome challenges derived from decentralised infrastructures, inadequate knowledge sharing, financial risks and regulatory uncertainties. Sharing of information, results and rewards are key factors in the success of multilateral partnerships. The tendency for closer collaboration across previously well-defined borders is also mirrored by the increasing number of horizontal alliances in which the pharmaceutical industry is involved as it diversifies from traditional, vertical modes of operation.

Respecting patient values and interests in research strategies and regulatory frameworks is an imperative. Creating the conditions for translating promising therapeutic options into "first-in-human" studies is one of the biggest challenges in health innovation for Alzheimer's disease. Issues include: patient selection and stratification, the voluntary involvement of well-informed patients, and protection of privacy/confidentiality to prevent unauthorized or inappropriate use of personal information. Patient organisations play a significant role in global Alzheimer's trials to address ethical, legal and regulatory issues, to support patient recruitment and retention in long-term clinical trials and to provide input to regulators assessing the risks and benefits of approving proposed new medicines. Transparency and communication are the cornerstones of mutually agreed and effective research and health policies. They help to meet information needs along the value chain of innovative research strategies and the development of future medicines for Alzheimer's disease and other dementias. It will be of importance to deepen the involvement of people living with dementia in research and drug development processes; there is a need for a strong evidence base in what is communicated to patients. Governance structures would be needed to ensure an efficient communication with the public about the current and future potential of diagnostic tools and medicines for Alzheimer's disease and other dementias.

Phyllis Barkman Ferrell stated that the huge societal impact of Alzheimer's disease and other dementias is well recognised and tackling it requires a collaborative effort by all relevant parties. As our understanding of the underlying pathology of Alzheimer's disease has increased, the scientific community largely agrees on the need to diagnose and manage Alzheimer's disease at an earlier stage in the disease process. In this paradigm, the use of new potential disease-modifying therapies in patients with mild Alzheimer's disease, or even in earlier stages, could complement existing and new symptomatic therapies and fundamentally change the face and societal burden of the disease.

In parallel to therapeutic innovation, health systems need to be prepared to accommodate the future universal use of Alzheimer's diagnostics and therapies. Limited financial resources and rising

pharmaceutical investments (OECD, 2015c) have caused innovators, policy makers, payers and civil society organisations to move closer together and to share resources and risks in order to manage the economic implications of Alzheimer's disease and other dementias. There is broad agreement that research and health innovation can provide governments and other payers with the adequate tools in order to manage rising health care costs and to increase the health and wellbeing of ageing populations (OECD, 2015d). Advances in biotechnology, nanotechnology, and information and communication technologies (ICTs) are key to address health and care challenges, but often come with substantial resource needs.

"The emergence of parallel qualification advice between the FDA and EMA has been a major recent development and has proved to be a mutually beneficial and fruitful collaboration. We should not forget that patients' representatives are involved in scientific advice and qualification procedures of clinical outcomes and/or biomarkers." (Dr. Maria Isaac)

Marc Wortmann presented the efforts by Alzheimer's Disease International (ADI) to strengthen the involvement of the dementia community in research and drug development. The project was initiated after discussions at G7 event in London (2013) made it clear that there is a need for an awareness campaign among people living with dementia and their families.

There is a great interest by individuals to actively participate in clinical trials. However, finding information about clinical research programmes remains a significant challenge for the concerned public. One major issue is that often sponsors do not update the information provided on trial registries such as on clinicaltrials.gov. A recent report from the UK Office of Health Economics[ix] pointed out that there is limited information about trials that were discontinued (stopped prematurely). Of those that did explain, difficulty in recruiting was reported as one of the main reasons for discontinuation. This is one of the reasons research and development costs for Alzheimer's disease and dementias are higher than other disease areas.

However, this difficulty in recruitment runs counter to the ADI experience and with what has been articulated in the Lausanne Dialogue: Individuals are eager to actively participate in studies, but lack guidance and information. This communication and logistical gap is now being addressed through the ADI Global Awareness Campaign on clinical trials, aiming at all member countries and especially those that have limited resources. ADI will lead this important process and share information about the diverse clinical trial registries and other relevant details on a dedicated website.

We need to make clinical trials more dementia friendly and learn from experiences of people who participate in studies and who could act as an ambassador for others. Therefore, trial site staff need to understand dementia and how information should be communicated: clearly and with repetition, when needed. It is also important to take expectations seriously. Questions about possible therapeutic effects must be addressed immediately and continuously during the trial. Several examples can be used as a reference for future clinical research in Alzheimer's disease and other dementias: TrialMatch[x] and the Brain Health Registry (United States), JoinDementiaResearch[xi] (United Kingdom) and other initiatives in Sweden and The Netherlands. The University of New South Wales in Australia is scoping the registries and aims to provide guidance for countries that want to start or improve.

"ADI is pleased to participate in the series of Lausanne workshops and to be a partner of the continuous Lausanne dialogue. The dementia problem is too big for one partner to solve!" (Marc Wortmann)

Significant investments are ongoing to accelerate drug development from the perspective of biomarkers and randomized clinical trial designs (e.g., validated endpoints) in Alzheimer's disease. However, as stated by Dr. Frederic de Reydet de Vulpillieres, relatively little has been done to facilitate the collection and analysis of high quality real world evidence (RWE).

The 'Real World Outcomes Across the Alzheimer's Disease Spectrum' (ROADS) project – part of the IMI-2 Call 6 launch in October 2015[xii] – proposes to develop and enhance public-private collaborative research programs to generate Alzheimer's disease-relevant health and social care data to provide recommendations on methods and measures to optimise prospective data collection reflecting appropriate Alzheimer's care and prevention. This first stage of a longitudinal project is aimed at informing a follow-on project to initiate prospective data collection and database improvement efforts for RWE.

The objectives of the ROADS to Better Care consortium (first project phase) are:

- Define a minimum set of measurable patient relevant real world outcomes. These outcomes should be aligned among key stakeholders on their relevance for different purposes (e.g. academic research, regulatory, health technology assessment (HTA), funding and reimbursement, relative effectiveness assessment, clinical guidelines and optimization of healthcare systems);

- In collaboration with national health authorities, HTA, and regulatory agencies, develop recommendations on appropriate Alzheimer's disease-related cognitive, functional, and behavioural endpoints that can be used across various types of real-world research programs and data systems outside of clinical trials;

- Identify data sources and outline a data strategy (including data aggregation and gaps in data), to characterize the spectrum of Alzheimer's disease across disease stages and multiple geographies and identify best practices in collecting real world clinical outcomes;

- In collaboration with patients and caregivers, identify new methods and technologies for incorporation into clinical and social care practice that would facilitate collection of patient/caregiver-centred outcomes;

- Provide recommendations of different approaches to model disease progression depending on data sources to enable better treatment selection and improved health care value for Alzheimer's disease.

During the project, data analyses and generation of hypotheses and modelling will be conducted with existing data from public and private consortia members.

Dr. Kristin Kahle Wrobleski further explained that the results of ROADS (first phase) will inform a second, separate project (timing to be defined). This second phase will involve prospective data generation which may include, but not be limited to:

- Closing data gaps on Alzheimer's disease in the real world of heterogeneous populations;

- Further develop patient relevant outcomes in real world settings;

- Deliver RWE with high quality standards that are recognized and accepted by industry, regulators and HTAs to support the evaluation of emerging Alzheimer's interventions; and

- Help optimize healthcare systems for better Alzheimer's -related care.

Selection of the partnering consortium will occur in early 2016, with an anticipated start date in the fourth quarter 2016.

Demonstrating value and cost effectiveness on the path to universal access

Box 6. Key messages: demonstration of value

- For patients and caregivers quality of life is the most important outcome measure; however most clinical trials and value frameworks are not designed to monitor and assess an impact on quality of life. We need dementia-specific measures of quality of life that can be implemented into research and reimbursement processes.
- The direct medical costs (hospital visits and primary clinical services) of dementia is important, but only a fraction (14%) of the full cost burden per person with dementia in our society which includes: 43% direct social care (nursing homes, social service visits to homes), and 43% unpaid care giving (loss of productivity) by spousal care or from other family members.
- Alzheimer's disease and other dementias affect individuals and their families at the same high rate – governments and payers should adopt a societal point of view of Alzheimer's disease in order to capture the full extent of the public health issue.
- Is society putting a priority on Alzheimer's disease? Societies should decide which diagnostics and therapies are critical for public health and should be reimbursed. We need to learn from other disease areas, such as oncology and HIV, and implement sustainability measures into development, commercialisation and access to future therapies for Alzheimer's disease and other dementias.
- Planning ahead: Do we have a health system and market place that is ready to support a preventive or disease modifying drug for Alzheimer's disease? Given the extent of the dementia challenge and its economic impact, governments are urged to develop reimbursement policy frameworks that foster continuous innovation in drug development.

The ageing of our societies is one of the greatest achievements of research, therapeutic innovation and sustainable public health systems. At the same time older people have to cope with more chronic diseases, a situation known as multi-morbidity that poses challenges to health systems to various degrees (OECD, 2011). The economic and societal impact of Alzheimer's disease and other dementias is enormous: During the last 5 years the global societal economic costs of dementia have increased by approximately one third and will most probably reach USD 1 trillion by 2018 (Alzheimer's Disease International, 2015). Because of increasing prevalence and cost of Alzheimer's disease, and because of the limited resources, these costs are simply unsustainable. Thus, it is our obligation to critically assess any intervention from a cost-effectiveness viewpoint (Wimo et al, 2014). Rising therapeutic costs have led stakeholders to demand more evidence of comparative or cost effectiveness for new drugs. In terms of financial burden, the global cost of dementia is well over half a trillion US dollars each year – roughly equal to the GDP of Switzerland. Informal care almost matches the costs of direct medical and long-term care of dementia. In the US alone out-of-pocket spending has been estimated at USD 44 billion, or 19% of total payments in 2015 (Alzheimer's Association, 2015).

"Dementia is a global health emergency. Low and middle-income countries will have the largest amount of burden, but the least amount of resources to fight the disease and societal impact." (Dr. Shekhar Saxena)

There is a need to develop adequate policy frameworks that balance efficiency of pharmaceutical innovation with sustainable public health systems. Also, timeliness of intervention is likely to have an important impact on the cost-effectiveness of both current and future treatments. Healthcare policy should aim to optimise the timing of Alzheimer's diagnosis, which is likely to necessitate detecting and treating patients several years prior to current clinical practice (Barnett, Lewis, Blackwell, Taylor, 2014). A variety of efficiency-oriented measures have sought to improve the broader access to effective diagnostics and therapies while limiting the rate of growth of health system expenditures (Winblad, Amouyel, Andrieu et al. 2016).

Payers should take into account that dementia is more than an isolated health issue; dementia affects the whole life of people and families so that the financial impact is bigger than just the cost of a drug, much bigger. (Tania Dussey-Cavassini)

Defining value of Alzheimer's diagnosis and treatment

This section addresses key issues in understanding the evidence and tools needed to support the innovator, manufacturer, regulator and the payer in defining the value of a potential therapy for Alzheimer's disease. The question remains as to whether the required healthcare infrastructure is in place in order to manage the global burden of dementia. Experts have discussed strategies to translate promising research and development efforts into effective and cost-efficient therapeutic solutions.

"It is crucial that we identify diagnostic and treatment paradigms that meaningfully impact the cognitive and functional deficits associated with progressive Alzheimer's disease. This impact may come via delayed onset, slower decline, or actual improvement to regain a prior, higher level. Reaching the eventual solutions requires integrated comprehensive strategies to find answers to significant outstanding questions." (Dr Louis Jacques)

Prof. Dr. Anders Wimo argued that people with Alzheimer's disease and other dementias may live decades from the early preclinical stage to the end stage. When new therapies for Alzheimer's disease are launched it is thus not possible to analyse the long term cost effectiveness of such interventions via conventional randomised clinical trials. A range of measures, such as pragmatic trials, observational studies, registry data and economic simulations need to be used. Furthermore, to make a judgement regarding long term cost effectiveness, it is also necessary to have knowledge of the natural course of Alzheimer's disease in terms of progression and survival time. The sources for such data are observational studies and to some extent registries. Currently, much of the available data is outdated, making it difficult to draw relevant conclusions. Recent studies regarding incidence, prevalence and survival indicate a dynamic pattern with hopes for prevention approaches that will significantly delay or actually prevent symptomatic Alzheimer's – managing the disease much like HIV/AIDS or many cancers. Many studies and projects are now ongoing in Europe with a potential to update patterns of progression, survival, resource use and costs.

Prof. Dr. Anders Wimo further discussed that although there have been several failures; there are still many drugs in pipeline with a potential of disease modifying effects on the course of Alzheimer's disease. If such drugs enter the market, several challenges may occur:

- First, treatment with such drugs is likely to be costly, and will need to start early (pre-dementia or pre-clinical) in Alzheimer's disease, while the long term benefits in terms of costs and outcomes will occur later. An early diagnosis of Alzheimer's disease is also crucial, but currently diagnosis rates and certainty are low. The accuracy of the diagnostic

process in terms of positive and negative predictive values, and the risks for false positive and negative cases must also be addressed, in order to realize the benefits of an eventual treatment.

- Second, while the medical sector assumes the cost burden of such drugs, the social sector (nursing homes, home services, etc.) will realize most of the benefits; creating misaligned incentives. It is thus necessary to adopt a societal viewpoint for the discussions of cost-effectiveness and reimbursement of new treatments.

- Third, the long term effects on survival as well as on disease progressions are also difficult to predict, making economic modelling necessary when new intervention approaches of Alzheimer's disease and other dementias (prevention, disease modifying treatments) are evaluated.

The efficiency of drug development programmes and the effectiveness of therapeutic interventions are strongly linked with a reliable diagnosis of Alzheimer's disease and other forms of dementia. Reliable and accessible diagnostic criteria form the basis of any clinical trial – for the stratification of volunteers (enrichment of clinical trials), the definition of endpoints (criteria of success and failure), and the ultimate use of the potential therapeutic intervention (dosing regimen). For people affected by dementia, an early diagnosis may help to improve access to specific care services and symptomatic treatments; manage vascular and other high risk factors and comorbidities; incentivise participation in clinical trials; and to enable decision making before more significant cognitive decline inhibits the ability to make informed choices (Rubinstein et al., 2015). However, there has been a controversy about the magnitude of benefit conferred to individuals through early diagnosis and access to clinical and care services in the absence of effective, disease-modifying treatments (Wimo et al, 2014).

Ensuring high diagnostic accuracy is an important goal in Alzheimer's disease in order to achieve improved long-term outcomes; evidence about the amyloid status leads to significant changes in patient management, for example an earlier counselling and prescription of more appropriate drugs. However, there remains room for diagnostic improvement to Alzheimer's diagnosis in the clinical setting (Vandenberghe, Adamczuk, and Van Laere 2013).

Given the magnitude by which healthcare costs, the quality of life and disease progression change after an early diagnosis and adequate intervention, it has been suggested that economic studies of diagnostic impact would be warranted for the any future drug candidate (Fox, Lafortune, Boustani, Brayne, 2013).

From an innovator's perspective Dr. Ludger Dinkelborg laid out the significant role of molecular imaging in Alzheimer's disease diagnosis. It allows a non-invasive assessment of biological and biochemical processes in the brains of living subjects. Positron Emission Tomography (PET) imaging[xiii] has the potential both to enhance our understanding of Alzheimer's disease and to aid decisions to select candidates for drug development. Further, non-invasive amyloid PET represents a major advance in the clinical assessment (diagnosis) of cognitively impaired patients. Enabling for the first time in vivo detection of neuritic plaques (also known as senile plaques), a core element of Alzheimer's disease neuropathology, beta-amyloid PET imaging is adding cost effective value to the diagnostic process in Alzheimer's disease.

Amyloid imaging ensures a more accurate and faster diagnosis that leads to more confidence in choosing appropriate treatments; it may offer, especially in mild cognitive impaired subjects, valuable

information that helps predict the future evolution of the disease; it enables the selection of amyloid positive patients to be enrolled in clinical trials of disease modifying drugs at an early stage of the disease. However, despite this important innovation value, and years after approval, there is very limited reimbursement for amyloid PET imaging. Patients are still facing all the challenges of uncertain diagnosis and late or inappropriate treatments.

In a cost saving driven approach, decision makers, before deciding on reimbursement, want to see evidence that the impact of innovative diagnostics, such as amyloid PET imaging, improve health outcomes. However, this approach does not take into account two important factors: firstly, not all forms of the disease may benefit from treatment, but an accurate diagnosis is still essential in order to differentiate different types of dementia and manage the patient in the most appropriate way; secondly, without amyloid PET molecular imaging the research on drugs that change the course of Alzheimer's disease would not be possible – demonstrating that amyloid PET imaging has a value beyond the impact on health outcomes in the short term.

The question remains as to how we can find a solution to the payers' dilemma between investing in the potential value of innovation and waiting for real world evidence of improved health outcomes? The US has adopted an approach called Coverage with Evidence Development (CED). This is a controlled way to generate additional data concerning the utility and cost effectiveness of amyloid PET scans before a final decision to reimburse patients for the cost of using this diagnostic test In this context the The Imaging Dementia—Evidence for Amyloid Scanning (IDEAS) Study will establish an open-label, longitudinal cohort study to assess the impact of amyloid PET on patient outcomes. The study will be performed in accordance with the Center for Medicare & Medicaid Services (CMS) policy of Coverage with Evidence Development (CED) in Medicare beneficiaries who meet the Appropriate Use Criteria (AUC) for amyloid PET (Johnson et al. 2013). Our hypothesis is that amyloid PET will decrease uncertainty and increase confidence in the underlying cause of cognitive impairment, that this will translate into earlier counselling and interventions in these domains, and that these interventions will lead to improved outcomes.

The IDEAS Study is an observational, open-label, longitudinal cohort study designed to assess the impact of amyloid PET on patient-oriented outcomes in Medicare beneficiaries with mild cognitive impairment (MCI) or dementia of uncertain etiology. The study falls under the Centers for Medicare & Medicaid Services (CMS) Coverage with Evidence Development (CED) policy. A total of 18,488 Medicare beneficiaries meeting Appropriate Use Criteria (AUC) for amyloid PET will be enrolled over 24 months at sites throughout the United States. Dementia specialists will team with PET facilities able to perform amyloid PET and with trained radiologists/nuclear medicine physicians, all of whom will consent to completing the data requirements and timelines for the study. Amyloid PET will be performed and interpreted at each facility with results provided to the ordering physician for support in further clinical decision making, which will be captured for the study.

The over-arching hypothesis is that, in diagnostically uncertain cases, knowledge of amyloid status as determined by amyloid PET will lead to significant changes in patient management, and that this will translate into improved long-term outcomes. However, one limitation is that this lengthy study approach does not permit reimbursement for use of amyloid PET imaging in general clinical practice, with the consequence that only the patients enrolled in the study, or those persons capable of paying for this expensive test out-of-pocket will have access to the diagnostic capabilities of amyloid PET scans in the United States.

Dr. Ludger Dinkelborg concluded that in Europe stakeholders are taking first steps in adopting CED schemes, but there is still a long way to go. We need urgently to:

- Invigorate the systematic consideration of CED in coverage policies;
- Establish clear CED selection criteria and processes;
- Define new models to fund and incentivize CED studies;
- Identify and apply appropriate study methodologies;
- Apply new generated evidence in systematic and timely manner to inform coverage decisions.

“Without payer’s recognising the crucial value of biomarkers and amyloid beta imaging in this devastating disease the incentives for investment and spending resources will vanish.” (Dr. Ludger Dinkelborg)

Planning for access

A vital step towards stopping Alzheimer’s disease is to ensure universal access to affordable, high-quality healthcare, therapies and diagnostics. This responsibility belongs to all stakeholders. As innovations reach the market, the ability to address the huge unmet needs in Alzheimer’s disease depends on the ability of pharmaceutical companies, diagnostic developers, payers and policy makers to agree on the value of treating, caring and supporting those living with the disease.

Cost-benefit measures are gaining importance for the regulatory assessment and marketing approval of therapies. Besides the assessment of efficacy and safety parameters, the successful investment in and development of innovative medicines requires a predictable pathway for reimbursement and payment. Someone has to pay for the first generation of innovative medicines in order to generate the incentives to develop subsequent improvements. The redistribution of the financial risks require a balance between producers (researcher, manufacturer) and purchasers (insurer, patients) that will help to support innovative research, access to medicines, rational use and cost containment. Policies to support price transparency and the measurement of therapeutic effectiveness can help to assure value for money and the responsible use of limited resources. As an actual example of how governments recognise the need for innovative medicines the recent programme of the Netherlands Presidency of the Council of the European Union examined ‘how new innovations could reach patients faster at a socially acceptable cost’ (Dutch Ministry of Foreign Affairs, 2016).

As stated by Phyllis Barkman Ferrell, for those patients who do receive an Alzheimer’s diagnosis, an integrated and holistic patient care system is not uniformly in place to ensure that patients flow through the system from primary care to other important care settings. Of equal importance, providers in clinical practice and patients/caregivers are not generally informed of opportunities for clinical trial participation, which offer potential access to innovative therapies not yet available through the clinic and speed the evaluation of new investigational therapies. Despite the unmet needs in Alzheimer’s therapy and disease management, recruitment to Alzheimer’s clinical trials is notoriously slow.

"In a few years we will see the first disease-modifying treatment on the market; it is a moral imperative to offer this to patients and to build the right health care systems around effective and universal patient access to the means of preventing or treating their disease" (George Vradenburg)

Phyllis Barkman Ferrell highlighted the need that pharma, regulators and payers must work together with health care providers to ensure that the local health care system is ready to embrace a new treatment paradigm; that is, a broader and more proactive approach that takes advantage of what is currently known about Alzheimer's disease pathogenesis and interventions and ensures access for the patients that are most likely to benefit. Future Alzheimer's disease management should encompass symptomatic treatment of patients with moderate and severe dementia and use of disease modifying therapies for those patients in the disease's early stages to prevent appearance of symptoms in patients with prodromal Alzheimer's disease, and prevent worsening of symptoms in patients with mild cognitive impairment (prodromal Alzheimer's disease) or mild Alzheimer's dementia.

The shift will be gradual, but can still benefit patients, even before a new therapy is approved. Success will depend upon:

- Raising awareness of Alzheimer's disease and its impact on society;
- Engaging of health care providers, the general population and other parties;
- Enabling a timely and more definitive diagnosis of Alzheimer's disease through increased availability and access to accurate diagnostic tools; and,
- Establishing healthcare systems that support information sharing and timely patient referral in order to reach the right patients, with the right therapies, at the right time.

"It was the creation of UNAIDS that made the difference in HIV – we need a similar step in order to make dementia a high priority at governmental level." (Dr. Thomas Zeltner)

In his presentation, Dr Louis Jacques expressed the view that the positive engagement of public and private health insurance payers is hindered by these current open questions and compounded by the persisting scientific uncertainty about the fundamental pathophysiology of Alzheimer's disease and its precise role as a sign or cause of specific clinical deficits. We can predict that the costs will be enormous, whether they are invested in patient management strategies with proven benefit or misapplied in the pursuit of ultimately unproductive therapeutic hypotheses. Payer confidence is implausible in this setting, and this uncertainty limits any enthusiasm among most insurers to accept these risks.

The historic construct of health insurance was not developed as a remedy for all social ills. It is rooted in the risk-based pooling of funds to pay for costs arising from specific health related conditions that are generally defined by a period or episode of illness. The extended period of preclinical and prodromal Alzheimer's disease, combined with the alternative causes for some cognitive and functional signals, can make it difficult to reliably identify the start of such an episode in a given patient. Remedies for the social burdens of Alzheimer's disease may fall to other public programmes outside of the health insurance paradigm, with different countries likely to develop different solutions that reflect their unique cultures.

Dr. Thomas Zeltner summarised the key evidence and tools needed to support payer evaluation in Alzheimer's disease and other dementias:

- The core payer responsibility is to manage the limited (financial and other) resources in the health care sector and to allocate them according to an accepted and transparent priority setting process;
- It is up to the government to decide where to allocate the limited competing resources. Since the prevailing value systems are very different in different countries, the process of priority setting and the outcome of this process is very different in different countries;
- In most countries the scope of the allocation is the total of the health care resources or overall financial resources (the health care budget). It does not take into account all the resources invested by patients and their families (nonprofessional and informal help). In Alzheimer's disease this is a substantial part of all resources spent. In a couple of countries there are initiatives to estimate the respective amount and to recompense it partially (with tax and/or premium money);
- In most high income countries health care costs are paid out of three pockets: taxes, premiums, and out-of-pocket payment. The fraction of each of these sources is different from country to country. For example, in Switzerland it about one third of each. There is a tendency in many countries to charge less to tax payers and more to premium payers and/or out of the pocket. The situation is much more difficult in low income countries where a more substantial part is financed out-of-the-pocket and therefore is less equitable;
- Science has an important role to play in the assessment where to invest. Efforts like the one of the National Quality Forum of the US (Priority Setting for Healthcare Performance Measurement: Addressing Performance Gaps for Dementia including Alzheimer's disease) are very welcome. The need to be followed by an appraisal tab the national level;
- Civil society and non-governmental organisations are critical for shaping the value discussion (e.g. how important is universal access to new Alzheimer's drugs in a country and society?) They are also crucial to advancing scientific knowledge and defending patients and their family's rights. All of this will have an impact on payer reflections and decisions.

Health status is often linked to productivity, income and capacity to participate. Due to inadequate health systems, developing and resource limited countries will be even more severely affected by the proportional increase of older people and dementia patients. Low- and lower-middle-income countries have a disproportionately high reliance on informal structures for care, compared with other nations.

REFERENCES

Alzheimer's Disease International (2015), *World Alzheimer Report 2015, The Global Impact of Dementia*, World Alzheimer Report 2015, http://www.alz.co.uk/research/world-report-2015

Barnett, J.H., L. Lewis, A.D. Blackwell, M.Taylor (2014), *Early intervention in Alzheimer's disease: a health economic study of the effects of diagnostic timing*, BMC Neurology, Vol. 14/101, http://dx.doi.org/10.1186/1471-2377-14-101

Dubois, B., H. Hampel, H.H. Feldman, P. Scheltens et al. (2016), *Preclinical Alzheimer's disease: Definition, natural history, and diagnostic criteria*, Alzheimer's & Dementia, Vol. 12, pp. 292-323, http://dx.doi.org/10.1016/j.jalz.2016.02.002

Dutch Ministry of Foreign Affairs (2016), *Programme of the Netherlands Presidency of the Council of the European Union*, http://www.consilium.europa.eu/en/council-eu/presidency-council-eu/

Fox, C., L. Lafortune, M. Boustani, C. Brayne (2013), *The pros and cons of early diagnosis in dementia*, *British Journal of General Practice*, Vol. 63/612, pp. 510-520, http://dx.doi.org/10.3399/bjgp13X669374

Gauthier, S., M. Albert, N. Fox et al. (2016), *Why has therapy development for dementia failed in the last two decades?*, Alzheimer's & Dementia, Vol. 12, pp. 60-64, http://dx.doi.org/10.1016/j.jalz.2015.12.003

Hampel, H., R. Frank, K. Broich. et al., (2010), "Biomarkers for Alzheimer's disease: academic, industry and regulatory perspectives", Nature Reviews, Drug Discovery, Vol. 9, http://dx.doi.org/10.1038/nrd3115

Hampel, H., S. Lista (2016), "The rising global tide of cognitive impairment", Nature Reviews Neurology, http://dx.doi.org/10.1038/nrneurol.2015.250

Nagandu, T., J. Lehtisalo, A. Solomon et al. (2015), A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial, The Lancet, Vol. 385/9984, pp. 2255–2263, http://dx.doi.org/10.1016/S0140-6736(15)60461-5

OECD (2011), *Health Reform: Meeting the Challenge of Ageing and Multiple Morbidities*, OECD Publishing, http://dx.doi.org/10.1787/9789264122314-en

OECD (2015a), "Enhancing Translational Research and Clinical Development for Alzheimer's Disease and other Dementias", OECD Science, Technology and Industry Policy Papers, No. 22, OECD Publishing, http://dx.doi.org/10.1787/5js1t57jts44-en

OECD (2015b), *Addressing Dementia: The OECD Response*, *OECD Health Policy Studies*, OECD Publishing, http://dx.doi.org/10.1787/9789264231726-en

OECD (2015c), *Health at a Glance 2015: OECD Indicators*, OECD Publishing, http://dx.doi.org/10.1787/health_glance-2015-en

OECD (2015d), *OECD Science, Technology and Industry Scoreboard 2015: Innovation for growth and society*, OECD Publishing, http://dx.doi.org/10.1787/sti_scoreboard-2015-en

Rubinstein, E., C. Duggan, B. Van Landingham, D. Thompson, W. Warburton (2015), *World Innovation Summit for Health (2015), A call to action the global response to dementia through policy innovation*, http://www.wish.org.qa/

United Nations (2015a), *World Population Prospects: The 2015 Revision*, Working Paper No. ESA/P/WP.241., Department of Economic and Social Affairs, Population Division, https://www.un.org/development/desa/publications/category/population

United Nations (2015b), *The 2015 Revision of World Population Prospects*, UN Population Division, http://esa.un.org/unpd/wpp/

Vandenberghe, R., K. Adamczuk, and K. Van Laere (2013), *The interest of amyloid PET imaging in the diagnosis of Alzheimer's disease*, Current Opinion in Neurology, Vol. 26/6, pp. 646-655, http://dx.doi.org/10.1097/WCO.0000000000000036

Winblad, B., P. Amouyel, S. Andrieu et al. (2016), *Defeating Alzheimer's disease and other dementias: a priority for European science and society*, Lancet Neurology, Vol. 15, pp. 455-532

Wimo, A., C. Ballard, C. Brayne, S. Gauthier, R. Handels, R.W. Jones, L. Jonsson, A.S. Khachaturian, M. Kramberger (2014), *Health economic evaluation of treatments for Alzheimer's disease: impact of new diagnostic criteria*, Vol. 275/3, pp. 304-316, http://dx.doi.org/10.1111/joim.12167

ANNEX 1 – BACKGROUND PAPER

CREATING A PROACTIVE AND PREDICTABLE PATHWAY TO TREATMENT AND ACCESS IN ALZHEIMER'S DISEASE: AN INDUSTRY PERSPECTIVE

Disclaimer

Please remember that this document may include input from representatives of companies that compete in the marketplace. Discussions, plans, consensus arrangement, agreements, strategies, etc., may be unlawful, if they relate to any of the following topics:

- Current or future prices or bidding information;
- Limits on production or product lines;
- Allocating customers or territories;
- Individual company marketing strategies, projections, or assessments;
- Establishing a practice of dealing with customers or suppliers.

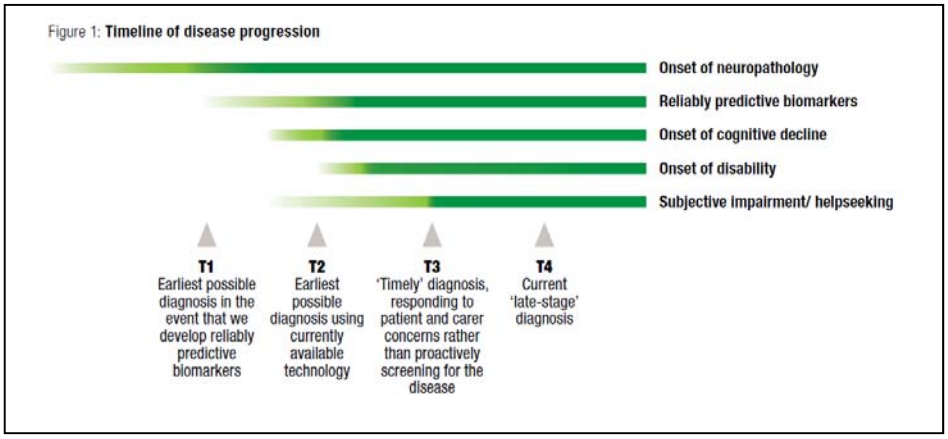
Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder. While disease pathogenesis is not fully understood, amyloid plaques and Tau tangles are considered hallmarks of disease (Hyman et al 2012). Additionally, there is increasing evidence that neuroinflammation also contributes to disease progression (Heneka et al 2015). Many believe that symptoms appear at least one to two decades after disease initiation. Although AD is a continuous, gradually progressive disorder, the National Institute on Aging and the Alzheimer's Association have recommended classification into stages (Albert et al 2011; McKhann et al 2011; Sperling et al 2011; Dubois et al 2009):

- Preclinical AD: biomarker evidence of AD pathology but clinically normal;
- Prodromal AD/mild cognitive impairment due to AD: biomarker evidence and cognitive symptoms with no or only subtle changes in function;
- Mild AD dementia: cognition continues to worsen, daily function begins to be impaired;
- Moderate AD dementia: cognition and function are more impaired and patient safety becomes a greater concern;
- Severe AD dementia: loss of most or all of ability to independently care for self.

Initial efforts in AD diagnosis and treatment development have focused on the most clinically evident stage of AD, dementia. In recent years, as the science has evolved, our understanding of the disease has increased considerably and the scientific academic community is aligned on the need to address the disease at earlier stages. However, while pre-symptomatic treatments may be in our near future, the challenges that exist with early diagnosis and treatment of patients with symptomatic disease remain a barrier to patients and their caregivers receiving the best possible care today. As shown in Figure 1. It is necessary to first move from T4 to T3 before moving to T2 or T1.

Figure 2. Figure 1. The importance of early diagnosis (Alzheimer's Disease International World Report, 2011).



The impact of AD and related dementias on society is well recognized. It is currently estimated that 46.8 million people worldwide suffer from dementia with an estimated global cost of dementia care at USD 818 billion in 2010 (Alzheimer's Disease International, 2015). By 2030 it is estimated that there will be 74.7 million people with the disease, and the cost of caring for people living with dementia worldwide could rise to around USD 2 trillion. By 2050, the estimated number of people with dementia will reach 131.5 million.

While current treatments remain vitally important to persons with dementia and their caregivers, there are currently a number of ongoing trials of new symptomatic treatments and potential disease-modifying agents. The findings from these trials will further inform the field in the next several years and hold the promise of significantly improving health outcomes for persons with AD. To pave the way for a new paradigm that employs symptomatic and/or disease-modifying treatments as soon as symptoms appear, if not before, pharma, regulators and payers must work together with health care professionals (HCPs) to ensure that the health care system is ready to embrace this new treatment paradigm. At the 2014 "Lausanne I" Conference, organized by the Organisation for Economic Co-operation and Development (OECD), Swiss State Secretariat for Education, Research and Innovation (SERI), Alzheimer's Disease International and The Global CEO Initiative on Alzheimer's Disease, we focused on the clinical trial and regulatory challenges to development of disease-modifying treatments. In this paper and at the 2015 "Lausanne II" Conference, we take a step further and provide an industry perspective on challenges in shifting the broader health and social care system mindset from only managing the disease in a later symptomatic stage (moderate and severe dementia) to a broader and more proactive perspective that takes advantage of what is currently known about AD pathogenesis and interventions - that is, an approach

inclusive of interventions to prevent appearance of symptoms in patients with prodromal AD, and prevent worsening of symptoms in patients with mild cognitive impairment or mild AD dementia.

The Current Paradigm for AD Management

"In high income countries, only 20-50% of dementia cases are recognised and documented in primary care. This 'treatment gap' is certainly much greater in low and middle income countries, with one study in India suggesting 90% remain unidentified." (Alzheimer's Disease International Dementia Statistics)

Current academic understanding of AD pathogenesis and management emphasizes the need for early detection but these scientific insights of the past decade have not yet translated into clinical practice or reached payers, policy makers and the general population. In clinical practice, diagnosis is occurring late in the disease process. It is only when cognitive and functional issues start to significantly impact everyday life that patients and caregivers might seek HCP consultation with concerns that their decline is not just the result of normal ageing. At this later stage, however, the patient may lack insight that something is wrong and, even when informed of this by a caregiver, may not seek treatment at all. Moreover, diagnosis may occur at a stage in the disease process when neurological decline may not be slowed, stopped or reversed.

For the HCP, the lack of consensus on the appropriate tools to detect/diagnose disease and the limited availability of treatments after diagnosis fosters a general reluctance to diagnose. Indeed, the wait and see approach (i.e., noting whether symptoms worsen over time) is a legitimate, albeit potentially fatal, method for confirming that disease has progressed.

For those patients who do receive an AD diagnosis, an integrated and holistic patient care system is not usually in place to ensure that patients flow through the system from primary care to other important care settings (including memory clinics). HCPs and patients/caregivers are also not widely informed of the importance and availability of increased socialization, dietary modifications, exercise, art programs, and cognitive therapy to improve or delay symptomatic progression. Patients/caregivers are also not typically made aware of the availability of the appropriate counseling needed to provide improvement in quality of life for both the patient and caregivers, long-term care options and legal, financial and end-of-life choices. Of equal importance, HCPs and patients/caregivers are not generally informed of opportunities for clinical trial participation, which offer potential access to innovative therapies not yet available through the clinic; despite the lack of approved treatments and huge unmet treatment needs in AD, recruitment to AD clinical trials, by HCPs or otherwise, is notoriously slow.

Obstacles to a More Proactive Management of AD

In this context, we define proactive management as striving to maintain brain health through early intervention and integrated care. This involves emphasis on lifestyle factors and treatments that target disease before symptoms appear, and in those patients with symptoms, helps manage symptoms and slow decline.

Education and Training

HCP understanding of disease process

The current understanding of AD pathogenesis by the research community has not effectively penetrated primary care practice, payers, policy makers, patients, and caregivers. In particular, within these groups, there is not always a complete understanding of the distinctions in terminology (e.g., dementia versus Alzheimer's disease, cognitive decline due to Alzheimer's versus 'normal' ageing), disease pathogenesis (including the fact that the disease process starts decades before symptoms emerge) and the mechanism of action of new AD agents.

Without broad dissemination and uptake of this basic knowledge of disease progression, new diagnostics and treatments designed to detect and influence the early course of disease and to deliver better outcomes may not be optimally integrated into the clinic and may face challenges as they relate to support by global health systems (coverage and payment).

Societal stigma

AD is seen as a disease with no hope. Many families, and even physicians, avoid using the words "dementia" or "Alzheimer's" in the presence of the patient. HCPs may be reluctant to diagnose AD and communicate the diagnosis to patients and families with the fear of doing more harm than good. Unfortunately, they see "hope" as the strongest tool in their AD tool box.

Timely Detection of Disease

Accuracy of diagnosis

Accurate diagnosis of AD remains a huge challenge. As already highlighted, the overwhelming concern is the large numbers of individuals with dementia (especially mild AD dementia) who have not been diagnosed and thus have not received available treatment and counselling on lifestyle factors that may slow decline in quality of life. In addition, inaccurate diagnosis is frequent. For example, ~25% of patients enrolled/screened for participation in AD clinical trials with a clinical diagnosis of AD made by experienced investigators had no evidence of amyloid plaques (Siemers et al 2015).

Detection of disease encompasses:

- Provisional assessment (screening) in the primary care setting , which includes detection of high risk individuals through absence/presence of known risk factors, as well as use of a validated cognitive assessment tool to aid with establishing a provisional diagnosis; and

- Assessment using more advanced diagnostic tools, most likely in a specialist clinic, for a more definitive differential diagnosis.

Tool availability

In clinical practice, current assessment tools measure cognitive and functional decline. They are thus most useful in symptomatic stages of disease, and, not infrequently, multiple assessments over time are required to detect progressive deficits. There are still no formal patient assessment processes in widespread use, nor are there widely accepted and accessible advanced diagnostic tools that accurately predict those individuals without symptoms but with early disease who are likely to develop symptoms. Moreover, the availability of accurate diagnostic tools is dependent upon a good understanding of disease pathogenesis, an area where there are still many gaps in our understanding.

Payer and Value-Based Evaluation

While regulators primarily evaluate the risk-benefit profile of new treatments, payers focus more on the cost-benefit profile. The development of new AD diagnostics and new treatments to slow progression of AD for use in patients with earlier disease will challenge existing payer value frameworks in several ways.

Access to diagnostics

Currently, payers define the 'value' of a diagnostic to the health system based on whether its use results in a change in clinical practice (i.e., whether the HCP provides different treatment) and in health outcomes for the patient. In the AD space, the currently-limited pharmacological treatment options make it difficult to demonstrate value of a diagnostic using this paradigm, particularly if the diagnostic is targeted to a patient population with early preclinical or prodromal AD for which no medications are indicated. Yet use of a diagnosis today, whether early or late in the disease process, will help patients and caregivers plan for future care and initiate lifestyle changes such as dietary modifications and exercise; this benefit is missed in the current payer value framework.

The current paradigm also limits the incentive to develop, and the ability of the health care system to anticipate, innovative treatments targeted at earlier stages of the disease where a timely and accurate diagnosis is essential.

Access to treatments

When considering costs, current payment paradigms typically focus 'value' assessments of new treatments within a framework of direct costs related to health care resource use (e.g., hospitalizations, medical events). In the case of new AD treatments, this approach fails to take into account either the significant proportion of costs related to informal caregiving or the slowly progressing nature of the disease with few distinct medical events. When new treatments are introduced that target earlier stages of the disease and are designed to prevent symptoms of the disease, patients are further from experiencing significant costs related to health system utilization, institutionalization or full-time care. The overall result of applying the current payment paradigm may well be that a payer (or payers more generally) are reluctant to make the up-front investment in the new AD therapies administered at earlier stages of disease because of uncertainty around the impact to downstream costs and benefits that may or may not be relevant to the payer's budget.

In addition to considering health care costs and resource utilization, payers consider the clinical value and benefit of treatments. Of particular relevance to payers are the effects of treatments on functional deficits. Since cognitive effects of the disease and of treatment are likely to precede the expected functional effects, showing functional benefit, particularly in patients with early disease where functional impairment is not yet apparent, may not be feasible. New disease-modifying treatments that target the underlying pathology of AD may have positive cognitive (or functional) effects due to a slowing of disease progression; however, unlike existing symptomatic treatments, they are not designed to improve cognition or function but to slow decline. If the payment paradigm does not take these points into consideration, showing benefit of disease-modifying treatments will be challenging.

Ongoing Work and Future Collaborations

In this section, we provide general and specific examples of how these obstacles can and are being addressed. This section is intended to encourage discussion and future collaboration; it is not intended to be comprehensive.

Create a Greater Sense of Urgency of the Problem

Emphasize that AD is a huge and growing socio-economic concern, with its impact reaching far beyond the health care system to caregivers and to society in general. Importantly, along with this, it needs to be clearly communicated that there is hope - that is, management options are available and will become increasingly available with well-framed innovation-oriented policies as well as more scientific opportunities and investments in drug development. Global momentum will grow with the increasing recognition that this is a shared problem requiring a shared solution. Examples are:

- The IMI2 Call on Patient Engagement (IMI2 5th call for proposals 2015), see below; and education through Ted Talks e.g., 2015 talk by Samuel Cohen, "Alzheimer's is not normal aging - and we can cure it".

- Identify health outcome and cost mitigation goals and drive global action to measure progress in meeting those goals. Disseminate quality measures to help in the understanding of gaps in care delivery;

- In 2014, the National Quality Forum (NQF) presented a conceptual measurement framework and multi-stakeholder recommendations for development of future performance measures focusing on patients with dementia and their caregivers (NQF 2014). Their report described priority areas for future performance measure development and included additional recommendations for dementia research and policy more generally.

Foster Information Sharing

Engage and educate HCPs regarding why recent advances in understanding Alzheimer's disease are relevant for their patients and treatment practices today. Include opportunities for general practitioners to become connected with the leading scientific researchers in the field.

Engage the general population to raise their awareness around AD and dementia – Extend the Dementia Friendly Communities (DFCs) movement to raise awareness and change perceptions of dementia. Examples are:

- The Heart Ring Movement campaign (Japan), The Dementia Friends program initiative launched by Alzheimer's Society (UK), the Dementia Friendly America initiative (US).

- Stimulate more discussion/earlier conversations between patients/caregivers and PCPs.

- Increase connections between clinical practice and research opportunities. The Gérontopôle in Toulouse was established to bring together research efforts and clinical activities in order to boost research, prevention and promote the health of older people (Gillette-Guyonneta and Vellas 2012). Through the Gérontopôle, a model has been established whereby patients flow from general practice to specialists to memory clinics/clinical trial sites in a defined process which includes screening and advanced diagnosis.

- Share information on health care infrastructures that are supporting early diagnosis and timely management. The Fundaciò ACE, Institut Català de Neurociencies Aplicades (Fundaciò ACE, Barcelona, Spain) has created a care model that integrates diagnosis, therapy, follow-up care, daycare, and a day hospital, and does so in the context of an active clinical research, community

outreach, and educational program (Boada et al 2014). There are similar efforts in countries both in Europe and around the world.

- The IMI2 Neurodegeneration Patient Access work stream (IMI2 5th call for proposals 2015) is a more encompassing example of fostering the development of a clinical environment that supports information flow and coordinated patient management. Via a consortium of industry, academia and third parties, the project aims to determine optimal health care and community engagement practices in the AD health care (and clinical trial) environments so that patient/caregiver resources can be maximized.

Facilitate Timely Detection and Diagnosis

Educate HCPs on currently-available tools (e.g., Mini-cog, AD8, GPCOG, Memory Impairment Screen) and encourage their use in primary care settings. In concert with this, inform HCPs on next steps for patients who show cognitive impairment (e.g., referral to specialist for formal diagnosis, enrolment in clinical trial, use of currently available management assistance).

Ensure that appropriately-sensitive cognitive assessment tests are available worldwide. The range of available tests should cover all stages of clinical disease, from mild cognitive impairment to more severe AD dementia.

Ensure acceptance of these standardized reimbursable tools as part of an annual mental health check-up visit to provide a greater systematic understanding of cognitive decline on a population basis, and to provide individual patient benefit by identifying cognitive impairment at its earliest stages. Examples are:

- In the US, Medicare added detection of cognitive impairment to the new annual medical check-up visit in 2011 and the Alzheimer's Association subsequently published guidance on the detection of cognitive impairment during this visit.

- In early 2015, the Gerontological Society of America's (GSA) Workgroup on Cognitive Impairment Detection and Earlier Diagnosis (GSA 2015) outlined a course of action for increasing the use of evidence-based cognitive assessment tools as part of the Medicare Annual Wellness Visit (AWV). The workgroup outlined a four-step process focused on i) PCP initiating and continuing conversations with patients/caregivers about memory-related signs and symptoms that might develop in older adulthood; ii) PCP assessing the patient using an appropriate cognitive impairment detection; iii) Advocating that Medicare beneficiaries who exceed threshold scores for cognitive impairment based on the cognitive assessment tools undergo a full diagnostic evaluation; and iv) Advocating that those diagnosed with Alzheimer's disease or related dementia be referred to all appropriate and available community services to learn more about the disease process and how to address the future with a dementia diagnosis.

Development and acceptance of and accessibility to diagnostic biomarker tools that can accurately diagnose AD and predict future cognitive decline. Some diagnostic biomarker tools that detect beta-amyloid deposition through PET imaging or CSF analysis have already received regulatory approval although not widespread payer support. In future, it may also be feasible to detect amyloid deposition through ocular scans and blood markers and this may be useful as a screening tool. Development of tools to monitor disease progression (e.g., biomarkers to measure Tau or oxidative damage and inflammation) will also be important.

Inform Payer and Value-Based Evaluation

Identify methods and measures to optimize prospective collection of data, including real-world evidence (RWE) data, which will address payer questions that arise with the shifting focus to proactive AD care. Once new disease-modifying therapies are available, this could include a commitment by the pharmaceutical industry and other key health care players to generate and evaluate long-term RWE data with the aim of providing additional meaningful health outcome endpoints (e.g., time to institutionalization). Examples are:

- The Real World Outcomes Across the AD Spectrum (ROADS) project(IMI2 6th call for proposals 2015) is a public-private collaborative research program that aims to optimize prospective data collection and improve database designs so that data systems can be built that will promote more efficient AD-relevant health and social care data generation

- The collaboration between The Global CEO Initiative on Alzheimer's Disease and Optum Labs brings together public and private payers, pharmaceutical organisations and non-governmental organisations to leverage data and improve understanding of disease progression and inform disease prediction.

Encourage collaborations between payers, academia, modelling experts, and the pharmaceutical industry to create a value framework that will appropriately take into account the impact AD has on society as a whole and the unique challenges of measuring benefit in a slowly progressing disease where early intervention precedes downstream, measurable impacts by many years.

Create precompetitive collaborations, including collection of quantitative data on patient/caregiver assessment of treatment benefit-risk that can contribute to a better understanding of what patients and caregivers value in a potential treatment. These results could be used to inform regulatory decision-making and to help define appropriate criteria for assessing the value of new therapies and determine reimbursement and patient access; example: The Coalition Against Major Diseases (CAMD) is public-private partnership of pharmaceutical companies, research foundations, patient-advocacy groups, health organizations, and regulatory agencies, established by The Critical Path Institute and aimed at creating new tools and methods to enhance the development of new treatments for AD (as well as Parkinson's disease). The consortium focuses on sharing precompetitive patient-level data from the control arms of legacy clinical trials, developing new tools, and developing consensus data standards.

BIBLIOGRAPHY

Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's Dement. 2011;7:270-9.

Alzheimer's Association (2015), Alzheimer's Disease Facts and Figures, Alzheimer's & Dementia, Vol. 11/3.

Alzheimer's Disease International World Report, 2011. Available at: https://www.alz.co.uk/research/WorldAlzheimerReport2011.pdf.

Alzheimer's Disease International World Report, 2015. Available at: http://www.alz.co.uk/research/WorldAlzheimerReport2015.pdf.

Alzheimer's Disease International, 2015. The Global Impact of Dementia - An analysis of prevalence, incidence, cost and trends. Available at: http://www.alz.co.uk/research/world-report-2015

Alzheimer's Disease International. Dementia statistics. Available at: http://www.alz.co.uk/research/statistics.

Boada M, Tárraga L, Hernández I et al. Design of a comprehensive Alzheimer's disease clinic and research center in Spain to meet critical patient and family needs. Alzheimer's Dement. 2014;10:409-15.

Cavedo, E., S. Lista, Z. Khachaturian et al. (2014), The Road Ahead to Cure Alzheimer's Disease: Development of Biological Markers and Neuroimaging Methods for Prevention Trials Across all Stages and Target Populations, Journal of Prevention of Alzheimer's Disease, Vol. 1/3, pp. 181–202. http://dx.doi.org/10.14283/jpad.2014.32.

The Coalition against Major Diseases (CAMD). Available at: http://c-path.org/programs/camd/.

Cohen S. Alzheimer's is not normal aging - and we can cure it. 2015 Ted Talk. Available at: http://www.ted.com/talks/samuel_cohen_alzheimer_s_is_not_normal_aging_and_we_can_cure_it?utm_campaign=social&utm_medium=referral&utm_source=t.co&utm_content=talk&utm_term=science#t-343935.

Cummings, J.L., T. Morstorf, K. Zhong (2014), Alzheimer's disease drug-development pipeline: few candidates, frequent failures, Alzheimer's Research & Therapy, Vol. 6/37, http://dx.doi.org/10.1186/alzrt269.

Dubois B, Picard G, Sarazin, M. Early detection of Alzheimer's disease: New diagnostic criteria Dialogues. Clin Neurosci. 2009, Vol. 11, pp. 135-9.

Geoffroy, P. (2013), "CNS Drug Liabilities in Early Phase Clinical Trials", *Applied Clinical Trials*, Vol. 22/5, www.appliedclinicaltrialsonline.com/.

The Gerontological Society of America Workgroup on Cognitive Impairment Detection and Earlier Diagnosis Report and Recommendations. Available at: https://www.geron.org/images/gsa/documents/gsaciworkgroup2015report.pdf.

Gillette-Guyonneta S and Vellas B. The Toulouse Gérontopôle Research Center: Report of Activities, 2007–2011. J Alzheimer's Dis. 2012;28:721-32.

Heneka MT, Carson MJ, El Khoury J et al. Neuroinflammation in Alzheimer's disease. Lancet Neurol. 2015;14:388-405.

Hyman BT, Phelps CH, Beach TG, et al. National Institute on Aging-Alzheimer's Association guidelines on neuropathologic assessment of Alzheimer's disease. Alzheimer's Dement. 2012;8:1-13.

Innovative Medicines Initiative IMI2 5th Call for proposals.2015. Document reference: IMI2/INT/2015-01343. Available at: https://ec.europa.eu/research/participants/portal/doc/call/h2020/h2020-jti-imi2-2015-05-two-stage-master-1/1662621-c5_imi2_c5_text_9_july_2015_en.pdf.

Innovative Medicines Initiative IMI2 6th Call for proposals. 2015. Document reference: IMI2/INT/2015-02065. Available at: http://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2Call6/IMI2_Call6_FINAL.pdf.

McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's Dement. 2011;7:263-9.

National Quality Forum 2014 National Quality Forum 2014. Priority Setting for Health care Performance Measurement - Alzheimer's Disease: Prioritizing Measure Gaps - Alzheimer's Disease and Related Dementias. Available at: http://www.qualityforum.org/priority_setting_for_health care_performance_measurement_alzheimers_disease.aspx.

Orrell, M., C. Brayne (2015), *Dementia prevention: call to action*, The Lancet, Vol. 386, pp. 1625.

Siemers ER, Sundell KL, Carlson C, et al. Phase 3 solanezumab trials: Secondary outcomes in mild Alzheimer's disease patients. Alzheimer's Dement. 2015 [Article in Press]. doi: http://dx.doi.org/10.1016/j.jalz.2015.06.1893

Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's Dement. 2011;7:280-92.

ANNEX 2 – WORKSHOP PROGRAMME

The workshop will provide an international forum for stakeholders to articulate achievements and opportunities in biomedical research and health innovation for Alzheimer's disease and other dementias – aiming to address the challenges and barriers to the introduction into the market of effective treatments and diagnostics. Following on last year's conference, this year's will feature developments in regulatory and access pathways for potential innovations in dementia and the perspectives of regulators and payers, specifically the evidence and tools needed to support regulatory and payer evaluation of innovations. Stakeholders will discuss approaches to encourage more innovative research, shared governance, and health economic models.

Through an exchange to encourage innovation, representatives from governments, regulatory agencies, the research community, patient organisations, industry and insurers will discuss progress and future action in:

- The current therapeutic pipeline and progress on the path to 2025, including advancing patient focused drug development and implementing outcomes-based approaches in treatment;
- Implementing innovative biomedical research tools in product development and regulatory models, including the scope for adaptive regulatory processes, enhanced clinical trial designs and a strengthened diagnostic environment;
- The current state of biomarker evidence and research, and the required advances needed for regulatory use;
- Access to future therapies and diagnostics, including the evidence and tools needed by payers to ensure sustainability.

This workshop is a follow-up event to the OECD workshop on "Enhancing Translational Research and Clinical Development in Alzheimer's Disease and Other Dementia: The Way Forward" in Lausanne, Switzerland in November 2014 supported by the Swiss Government, The Global CEO Initiative on Alzheimer's Disease (CEOi) and Alzheimer's Disease International (ADI). It is intended to provide input to ongoing international policy discussions on Alzheimer's and dementia, including the work of the World Dementia Council, G7, OECD, WHO and others. More information on the OECD's work on dementia is available here: http://www.oecd.org/health/dementia.htm

Day 1 (15 December 2015)

Workshop Moderator: Isabella Beretta, Federal Department of Economic Affairs, Education and Research, Swiss State Secretariat for Education, Research and Innovation

- **Welcome and Opening Remarks**

  - Tania Dussey-Cavassini, Vice-Director General of Swiss Federal Office of Public Health, Ambassador for Global Health, Switzerland

  - Peter Schintlmeister, Chair, Working Party on Biotechnology, Nanotechnology and Converging Technologies, Organisation for Economic Co-operation and Development

  - Marc Wortmann, Executive Director, Alzheimer's Disease International

  – George Vradenburg, Convener, The Global CEO Initiative on Alzheimer's Disease, Member, World Dementia Council

- **Session 1 – Facilitating Drug Development –** Moderator: George Vradenburg, Convener, The Global CEO Initiative on Alzheimer's, United States

The past decade of research has failed to produce any new therapies to address the huge unmet needs of dementia prevention, treatment and care. Yet, we are possibly on the cusp of a wave of innovation as several rigorous research programs are nearing the conclusion of successful testing, raising hopes that innovative new approaches will finally reach persons with or at risk for dementia. The need to optimize the navigational path for assessing these interventions and their access to the market requires an understanding of the drug pipeline, the evidence needed by regulatory and payer authorities to review prospective interventions and the short, medium, and long-term strategies and associated stakeholder actions to deliver successful interventions to those with or at risk of dementia. The purpose of this session is to define what innovations are in development and what is needed to ensure these innovations reach the market.

  - **Innovation by 2025? A Review of Potential Future Therapies for Alzheimer's Disease**; Andrea Pfeifer, CEO, AC Immune

  - **Innovation in Prevention Therapies**; Tobias Hartmann, Professor, Director Deutsches Institut für Demenzprävention (DIDP)

  - **Building a 21st Century Global Clinical Trial Infrastructure**; Luc Truyen, Vice President, Neuroscience External Affairs & Chair, Global Fight Against Alzheimer's Disease, Janssen Pharmaceutical

  - **An Integrated Approach to Dementia Research**; Raj Long, Senior Regulatory Officer, Integrated Development, Global Health, Bill & Melinda Gates Foundation; Director Integrated Development – UK Department of Health; and Member of World Dementia Council Claus Bolte, Division Head, Clinical Review, Swissmedic

  - **The Perspective from PMDA: Japan's Leadership in Responding to Rising Impact of Alzheimer's Disease**; Yoshiko Komuro, Deputy Review Director, Office of New Drug II, Pharmaceuticals and Medical Devices Agency (PMDA), Japan

  - **A Perspective from Health Canada**; Emma Spreekmeester, Manager, Health Products and Food Branch, Health Canada, Government of Canada

- **Leadership from the World Health Organization**; Shekhar Saxena, Director, Department of Mental Health and Substance Abuse, World Health Organization

- **Session 2: Mobilising The Global Patient Community –** Moderator: Gautam Maitra, Head of Regulatory and External Affairs, AC Immune

In recent years a number of initiatives and national and international efforts have been undertaken to address the challenges in the field of dementia. Yet, the speed of the global response is going to be measured by the degree of international consensus, collaboration and shared action – and also the level of engagement of people living with dementia. The purpose of the discussion will be to increase understanding of the strategies and action plans to rally people, communities, countries and regions behind the global fight to stop dementia.

- **Living with Dementia**; Hilary Doxford, Alzheimer's Society, Research Network Volunteer; Member, World Dementia Council

- **Leveraging the Engagement of the Dementia Community into Research**; Leveraging the Engagement of the Dementia Community into Research

- **A Novel Patient/Caregiver Driven Research Network in Alzheimer's**; Meryl Comer, President, Geoffrey Beene Foundation Alzheimer's Disease Initiative

- **Big Data for Better Outcomes**: Frederic de Reydet de Vulpillieres, Director, Global Patient Access, Novartis Kristin Kahle Wrobleski, Principal Research Scientist, Eli Lilly and Company

- **Session 3: Improving How Biomarkers Get To Market –** Moderator: Husseini Manji, Global Head of Neuroscience, Janssen, Chair of the Foundation of National Institute of Health Neuroscience Biomarkers Consortium

Advances in the understanding of progression of dementia at the cellular and molecular levels have spurred new research approaches. New technologies will facilitate diagnosis of the disease and development of drugs for dementia. As the relationship between a class of drugs and a biomarker becomes better understood, there is hope that it will be possible to identify patients most likely to benefit from the drug at increasingly earlier stages of the disease. Early and frequent interaction between industry and regulatory bodies will ensure studies are appropriately designed and biomarker test performance is well characterized.

- **Biomarkers: Progress Towards Surrogate Markers for Measures of Drug Effect**; Philip Scheltens, Professor, Cognitive Neurology, Director, Department of Neurology and Alzheimer Center, VU University Medical Center

- **Improving Diagnosis**; Harald Hampel, Professor and AXA Research Fund-UPMC Chair at the Sorbonne Universities, Pierre and Marie Curie University (UPMC), Department of Neurology, Paris, France

- **Update on Prevention Studies**; Serge Gauthier, Director of the Alzheimer's Disease Research Unit, Medical studies at the Université de Montréal

- **Supporting Validation for Regulatory Use: An EU Perspective**; Maria Isaac, Senior Scientific Officer, European Medicines Agency (EMA)

- **Drug Development for Alzheimer's Disease: Lessons Learned from Current Immunotherapy Trials**; Roger Nitsch, Professor, University of Zurich

Day 2 (16 December 2015)

- **Keynote**: John C. Reed, F. Hoffmann-La Roche, Global Head of Pharma Research and Early Development; Member, Roche Corporate Executive Committee

- **Session 4: Ensuring Access to Future Therapies and Diagnostics –** Moderator: Heiner Sandmeier, Deputy Secretary General, Interpharma

A vital step towards stopping Alzheimer's disease is to ensure universal access to high-quality healthcare, therapies and diagnostics. This responsibility belongs to all stakeholders. As innovations make it to market, the ability to address the huge unmet needs in Alzheimer's disease depends on the ability pharmaceutical companies, diagnostic developers, payers and policy makers to agree on the value of treating, caring and supporting those living with the disease.

- **Demonstrating the Cost Effectiveness of Treating Dementias: Exploring the Process and Challenges**; Anders Wimo, MD, PhD, Adjunct Professor, Division of Neurogeriatrics, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet

- **How Will Value be Determined: European and US Perspectives on Treatment and Prevention**; Louis Jacques, Chief Clinical Officer, ADVI, former Director, Centers for Medicare & Medicaid Services' Coverage and Analysis Group

- **Evidence and Tools Needed to Support Payer Evaluation**; Thomas Zeltner, Board Chairman, KPT, former Secretary of the Health of Switzerland Federal Department of Home Affairs FDHA

- **Value of Treating Alzheimer's Disease: Innovators Perspective**; Chris Leibman, Vice President, Global Market Access, Biogen

- **Value of Early Diagnosis Alzheimer's Disease: Innovators Perspective**; Ludger Dinkelborg, Managing Director, Imaging Division, Piramal

- **Delivering Innovative Medicines – Is the Required Healthcare Infrastructure in Place?**; Phyllis Barkman Ferrell, Global Brand Development and Product Team Leader for Alzheimer's Disease, Eli Lilly

Session 5: Discussion; The Way Forward in Alzheimer's Disease and other Dementias – A conversation led by Dirk Pilat, Deputy Director, Science, Technology and Innovation, Organisation for Economic and Co-operation and Development and George Vradenburg, Global CEO Initiative on Alzheimer's Disease The purpose of this session is to gain the collective input of the Lausanne II workshop participants and define the actions that can be taken forward and the progress that can be made in 2016.

Closing of Workshop: Isabella Beretta, Swiss State Secretariat for Education, Research and Innovation.

ENDNOTES

i http://www.alzforum.org/

ii Alzheimer's Disease International, 2015; United Nations, 2015a; United Nations, 2015b

iii http://www.who.int/mental_health/neurology/dementia/call_for_action_en.pdf?ua=1

iv file:///C:/Users/Garden_h/Downloads/nationaal-programma-engels(2).pdf

v http://ec.europa.eu/health/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf

vi http://www.lipididiet.progressima.eu/

vii http://www.alzheimersanddementia.com/article/S1552-5260(14)02355-3/fulltext.

viii http://www.adni-info.org/.

ix https://www.ohe.org/publications/dementia-rd-landscape.

x http://www.alz.org/research/clinical_trials/find_clinical_trials_trialmatch.asp.

xi https://www.joindementiaresearch.nihr.ac.uk/.

xii http://www.imi.europa.eu/content/overview-imis-calls-how-participate.

xiii Positron Emission Tomography (PET) is a minimally-invasive diagnostic imaging procedure used to distinguish normal from diseased tissue in conditions such as cancer, ischemic heart disease, and some neurologic disorders. Amyloid PET uses a new class of radiopharmaceuticals that detect levels of amyloid in human brain. Measurements of cerebral amyloid may be clinically useful in the work up and management of patients with cognitive impairment who are being evaluated for possible Alzheimer's disease or other causes of cognitive decline.