PAVE

November 2019

FROM INNOVATION TO IMPACT

Introducing Project Alzheimer's Value Europe

A report summarising key insights from the work of the Pathways for the Introduction of Alzheimer's disease Treatments (PIAdT) Working Group and introducing opportunities for the new Project Alzheimer's Value Europe (PAVE) initiative to support timely access to forthcoming Alzheimer's disease innovations through improved models for value assessment and funding

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Foreword

Alzheimer's disease has been called the greatest health challenge of the 21st century—the disease is notoriously difficult to diagnose, exacts monumental costs on individuals, families, communities, and health systems, and has frustrated researchers looking for a disease modifying therapy for the past 100 years. Adding urgency to an already critical situation, the incidence of Alzheimer's disease is projected to quadruple by midcentury as populations age. Today, there are causes for hope. New therapeutic and diagnostic innovations are poised to enter the market within the next five-years, and there are 28 Phase 3 molecules undergoing clinical trials.[1] We also know more about the brain than ever before due to enhanced imaging technologies, and finally have the tools in hand to begin to understand the disease's etiology and natural progression.

However, serious challenges remain that will need to be addressed if these future innovations are to result in real-world patient access and outcomes. Early Alzheimer's detection remains difficult and out-of-reach for most—this presents a challenge, as the next generation of innovative disease modifying treatments and therapies for Alzheimer's disease are likely to be most effective for patients in the early, and potentially pre-symptomatic, stages of the disease. Further, new innovative treatments and diagnostics for Alzheimer's disease will challenge today's models for health technology value assessment and funding approaches. Providing access to and funding for future innovations in Alzheimer's diagnosis and treatment will require new models for measuring and assessing value that include the holistic and societal benefits of Alzheimer's disease treatments and diagnostics.

The Pathways for the Introduction of Alzheimer's disease Treatments (PIAdT) Working Group was created in 2018 to address these specific valuation and funding challenges in Europe. In November 2018, PIAdT convened an expert workshop to provide a venue for identifying barriers and potential solutions for enhancing health technology assessment (HTA) models to match the unique complexities of Alzheimer's disease. The findings of that workshop are captured within this report, and served as the basis for the launch of Project Alzheimer's Value Europe (PAVE), a new collaborative, multi-stakeholder forum for continuing PIAdT's work on the assessment of and funding for emerging Alzheimer's therapies and diagnostics.

Introduction

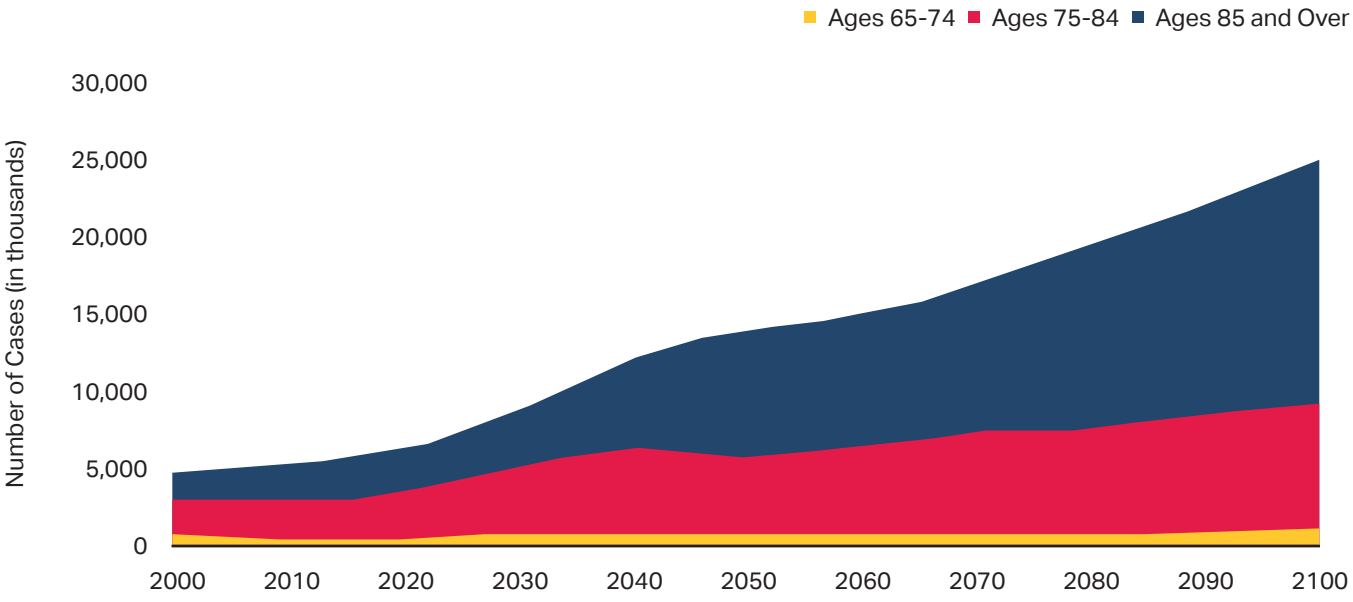
Alzheimer's disease is a neurodegenerative disease and the most common form of dementia. It progressively destroys brain cells, causes memory changes and loss, reduces cognitive capabilities and ultimately not only robs people with the disease of the potential to live fulfilled and independent lives, but also places a heavy burden on carers and the health systems.[2] Today, there are 50 million people living with dementia, globally,[3] and an estimated two-thirds of these people are living with Alzheimer's disease.[4]

The prevalence of Alzheimer's disease continues to grow as populations age and life expectancies increase. Barring major breakthroughs, the impact seen today is only a fraction of what will be realised in the coming decades, as incidences of the disease are expected to quadruple by midcentury.[5] Alzheimer's disease incidence in Europe is projected to increase by 87 percent between 2010 and 2050, with predictions suggesting that 16.5 million people in the region will be living with the condition by 2050.[6]

Alzheimer's incidence statistics bely the true number of people whose lives are impacted by the disease. Nearly one in three people over the age of 85 will develop some form of dementia, meaning that a growing portion of the population will spend their later years either living with Alzheimer's disease or caring for a loved one with the condition.[7] As such, the families of people living with Alzheimer's disease are faced with watching a loved one's decline, and are often devastated by the emotional and financial hardship that can often accompany a diagnosis.

Social carers, often family members of people living with Alzheimer's disease, play a central role within Alzheimer's care, yet the role is proven to exact a toll on carers' own health and well-being. For example, the physical health of an Alzheimer's carer is linked to the health of their loved one. According to a 2011 study, carers' health declines alongside the declining health of the Alzheimer's patient.[8] Carers also regularly report higher rates of insomnia, depression, and chronic illness than their non-carer peers,[9]

Figure 1: Projected Alzheimer's Disease Prevalence*, 2000-2100



* PhRMA projections calculated by applying current prevalence rates to population projections.

Data sources: U.S. Census Bureau[2]; Hebert et al.[3]

with one European study showing that 60 percent of carers surveyed had either depressive or anxiety disorder.[10] Carers comprise a significant number of the total population in Europe, with data derived from the European Quality of Life Survey estimating that there are about 100 million carers in Europe today, equivalent to about 20 percent of the population of the European Union.[11]

Globally, policymakers acknowledge that Alzheimer's disease is one of the costliest diseases to society—in 2018 alone, global dementia costs were estimated at US$1 trillion, and are projected to rise to US$2 trillion by 2030.[12] However, emerging research indicates that even these staggering numbers fail to capture the magnitude of Alzheimer's disease's true impact on economies and communities. For example, despite a general understanding that indirect costs borne by social carers are significant to the overall financial burden of Alzheimer's disease on society, the specific calculation of those costs is complex and challenging and many approaches may not adequately capture other financial impacts on households, such as reduced savings.[13] The projected cost-burden of Alzheimer's disease will likely increase exponentially as researchers begin to quantify the innumerable indirect and opportunity costs associated with the disease.

$1 trillion

in global dementia costs in 2018

35%

increase in global dementia costs between 2010 and 2015

1.09%

Dementia costs as part of global GDP

90%

of people living with dementia have at least one other chronic condition

Source: Brown J et al. "Association of comorbidity and health service usage among patients with dementia in the UK: a population-based study." March 2017. Link

34%

higher costs for managing comorbid non-communicable diseases in people living with Alzheimer's disease than in people without Alzheimer's disease

Source: Kuo TC et al. "Implications of comorbidity on costs for patients with Alzheimer's disease." August 2018. Link

Alzheimer's Treatments and Drug Development: Understanding Today's Landscape

Today's unmet need for Alzheimer's treatments is significant. Current treatments available include cholinesterase inhibitors for patients with any stage of Alzheimer's disease and memantine for people with moderate-to-severe Alzheimer's disease.[14] These medications have been shown to enhance the quality of life for both patient and carers when prescribed at the appropriate time during the course of illness; however, they do not change the course of illness or the rate of cognitive decline.[15] Practically speaking, this means that there are currently no treatments that cure, prevent, effectively treat, or slow the effects of Alzheimer's disease.

The first case of Alzheimer's disease was diagnosed over 110 years ago[16]—in the subsequent century of medical advances, the global community has made frustratingly little progress in developing treatments or cures for Alzheimer's disease, despite billions of Euros of investment by the private sector and significant public sector funding commitments globally. Developing Alzheimer's treatments, therapies, and diagnostics is uniquely challenging. Its etiology is not fully understood, identifying pre-symptomatic patients who fit the profile for emerging treatments is incredibly difficult, and researchers are faced with immense public pressure demanding treatment when "breakthroughs," even pre-clinical in nature, are reported.[17]

Nonetheless, decades of research have yielded valuable insights. Over the past decade, building on the findings from many large, global clinical trials, the focus of Alzheimer's drug discovery and development has shifted to intervening early in the disease to maximise impact on disease progression. These efforts have been coupled and enabled by advancements in diagnostics. Today's amyloid and tau PET scans—brain imaging tests used to identify Alzheimer's disease biomarkers[18]—can identify Alzheimer's disease in patients earlier than ever before and assist in measuring the efficacy of new treatments.[19]

The fiscal and human impact of Alzheimer's disease represents the challenge of our lifetime. It is not just a health challenge—it exacts a heavy toll at the individual, family, community, health system, and national level with real repercussions for the global economy.

There remains optimism about the promise of innovative medicines for Alzheimer's disease being introduced into the clinic in the near future. Based on the most recently available pipeline analysis, there are currently 28 Phase 3 agents that could reach the market in the next five years; and, of those, 11 are symptomatic drugs, and 17 are disease-modifying drugs.[20] Forthcoming innovative treatments and diagnostics for Alzheimer's disease will challenge the current approaches to value assessment, funding and reimbursement because health systems will desire to assess the long-term benefit of a new treatment based on the short-term efficacy demonstrated in clinical trials. Further, such treatments will shift some of the costs of Alzheimer's disease away from social carers and families and toward the health system. To that end, there remains a need to better understand how to assess the value of future Alzheimer's treatments and diagnostics so that forthcoming innovations ultimately result in real-life impact for patients and their carers.

OPPORTUNITIES TO INFLECT CHANGE

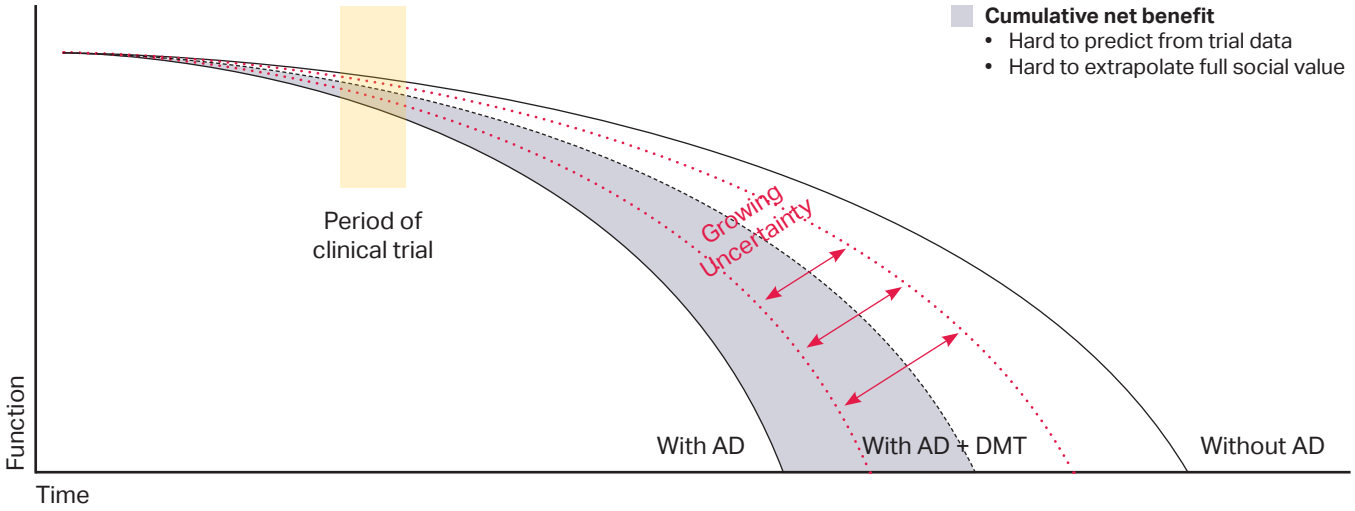
An Evaluation of Challenges to Valuing Alzheimer's Disease Innovations

A core challenge for valuing Alzheimer's disease therapies is the mismatch between the time horizon of clinical trial efficacy data—that is, two-to-five years—and the longer-term natural progression of the disease. Further, since it is likely that initial Alzheimer's innovations will target early, and potentially asymptomatic, stages of the disease, most of the benefits of treatment will derive from delayed disease progression and maintenance of cognition and function. Health technology assessment bodies have historically been less engaged in quantifying the benefits of prevention, and in calculating associated indirect benefits, such as reduced carer burden and lower societal costs.

"We need to understand the interactions between different aspects of care—drugs, doctors, hospitals, social care—but it is difficult to peg how a savings in one affects the others."

Participant, PIAdT Workshop, November 2018

Figure 2: An HTA Perspective on the Problem of Uncertainty Regarding Long-Term Treatment Benefit



THE CHALLENGE

Limited data available at launch on the long-term impact of treatment

While regulators will be asked to make licensing decisions for Alzheimer's therapies based on cognitive and functional endpoints from randomised control trials that follow patients for 18-36 months, the cognitive decline triggered by Alzheimer's disease ultimately progresses over decades. Meaningful value assessment needs to be based on an extrapolation of this data to a picture of the likely long-term impact of a new therapy on the disease's natural progression—and thus patient functional and cognitive ability—years into the future, along with the full range of benefits provided by the intervention.

Today's research on the natural history of disease and the early stages of Alzheimer's progression is limited. Absent a strong baseline understanding of the natural history of Alzheimer's disease and how that trajectory of cognitive decline compares to decline as a natural corollary of ageing, it will be difficult to calculate the net benefit of a treatment that delays the trajectory of cognitive decline but does not entirely prevent it. There is a lack of understanding around the triggers, causes, and progression of Alzheimer's disease—especially during its pre-symptomatic stages—rendering the development of sufficient baseline data for assessing future treatment impacts near impossible.

THE OPPORTUNITY

Enhance understanding of Alzheimer's' natural progression and develop new mechanisms for long-term evidence collection

In order to unlock the ability to effectively project the long-term efficacy of emerging Alzheimer's innovations, there is a need for an enhanced understanding of the natural history and progression of Alzheimer's disease. This need is especially urgent because the next generation of innovative disease modifying treatments and therapies for Alzheimer's disease are likely to be most effective for patients in the early, and potentially pre-symptomatic, stages of the disease. Nonetheless, even as understanding of the etiology and progression of Alzheimer's disease progresses, there will inevitably be degrees of uncertainty involved in developing forward-looking models at the time of a new therapy's launch. To address this unavoidable uncertainty, an evidence collection infrastructure could be developed to lay the groundwork for translating trial results into real-world evidence. This longitudinal data from the long-term, real-world use of new Alzheimer's innovations could provide ongoing supplementary insights on their ultimate efficacy.

Learning from the Multiple Sclerosis Experience

Early treatments for multiple sclerosis (MS) needed to be initiated as early as possible in the disease's progression in order to preserve functional abilities and neurological health; further, it was difficult for these treatments to achieve recommended by HTA bodies because of uncertainties in clinical trial data. To address this challenge, a risk-sharing scheme between the pharmaceutical industry, the UK Department of Health, and professional and patient groups was established. The collaboration supported studies to conduct long-term follow-up with a cohort of patients provided with first-generation treatments, providing real-world data on treatment efficacy over an extended period.

Source: Palace J et al. "Assessing the long-term effectiveness of interferon-beta and glatiramer acetate in multiple sclerosis: final 10-year results from the UK multiple sclerosis risk-sharing scheme." September 2018. Link

THE CHALLENGE

Significant portion of the value case for Alzheimer's innovations results from indirect benefits

As forthcoming innovations will target early stages of Alzheimer's disease, therapeutic benefits will derive from delayed disease progression and the preservation of patients' cognitive and functional abilities. Historically, health technology assessment agencies have not meaningfully addressed how to quantify the benefits of prevention, or how to calculate associated benefits such as reduced carer burden and lower societal costs. The extent to which evaluation bodies incorporate these factors varies by geography. Recently, health technology assessment bodies have demonstrated more interest in considering holistic benefits of new therapies, and increasingly have started to incorporate patient and carer inputs into their decision-making models. While this is a positive signal for the evaluation of new Alzheimer's disease innovations, there are remaining challenges in identifying a methodology and set of evidence to underpin a holistic approach to value assessment in Alzheimer's disease.

The challenge in developing a holistic valuation methodology is complicated by the fact that costs associated with new innovations will be immediate and borne by the health system, while benefits will manifest over a longer time horizon and will be shared among health care, social care, and informal care sectors. Complications and sensitivities abound in undertaking this type of impact evaluation work; for example, it can be difficult to quantify the direct linkage between Alzheimer's therapy and social care savings, and there is an ethical imperative to not build a model that treats caregiving as a burden that is relieved by the death of the patient.

THE OPPORTUNITY

Developing common, flexible, methodologies for assessing holistic value

Assessments for Alzheimer's innovations should reflect the diversity of the types of direct and, crucially, indirect benefits that new treatments and diagnostics accrue for individuals, families, communities, health systems, and economies. Further valuation assessment models will necessarily be flexible enough to grant appropriate consideration of the longer time horizon required for these benefits to be realized—especially in cases where therapy is initiated in patients during the pre-symptomatic stage of Alzheimer's disease.

Additional evidence on the broader burden of Alzheimer's disease on patients, carers, and economies will be needed in order to complement the data included in traditional assessment models if access is to be informed by a more holistic evaluation tool. In addition to benefits provided to patients and their carers, Alzheimer's innovations are expected to deliver monetary and non-monetary benefits both within and outside the health system. There is an opportunity for the valuation community to better understand the specific benefits of new therapies or diagnostics for assessment, such as reduced carer burden, delayed institutionalization, avoidance of lost workforce participation, and positive impacts on family and psychosocial health.

If models for measuring and assessing value exclude the holistic and societal benefits of Alzheimer's disease treatments and diagnostics, access to and funding for future Alzheimer's innovations will be a significant challenge.

OPPORTUNITIES TO INFLECT CHANGE

An Examination of Barriers to Adequately Funding Alzheimer's Disease Innovations

The identification and implementation of Alzheimer's disease funding models is urgently needed if health systems are to be able to respond to patient demand upon the identification of a successful new disease medication therapy. Treatment demands will be immediate, so health systems must begin to identify and lay the implementation groundwork for suitable Alzheimer's disease funding models that will cushion the budgetary impact of projected demand for Alzheimer's disease therapies and diagnostics. And, complicating matters, while social and political pressure for access to new therapies will likely be immediate, the provision of comprehensive evidence will not be—the direct and indirect benefits of Alzheimer's therapies will be realized over a time horizon of decades, as opposed to months-to-years. There is a need for new funding models that encompass a consideration of the holistic benefits of new diagnostics and therapies for Alzheimer's disease, and also provide a mechanism for dynamically revising access criteria as new evidence on efficacy or cost-effectiveness becomes available. While every country has its own specific context, priorities, and set of preferences for funding, identifying a subset of compatible funding approaches—including innovative options—will allow health systems to prepare for the access to and reimbursement of new Alzheimer's disease diagnostics and therapies.

310,000-750,000

Number of patients in the United Kingdom that would likely be eligible for Alzheimer's disease treatment, based on estimates from Alzheimer's Research UK

Source: Alzheimer's Research UK. "Thinking Differently: Preparing today to introduce future dementia treatments." March 2018. Link

THE CHALLENGE

New effective Alzheimer's innovations would spark immediate and sizeable expenditures for health systems

Introduction of a new Alzheimer's therapy will lead to significant year-over-year increases in spending demand that is not yet included in health system budgets. And, patient and health care provider demand for new therapies will likely be widespread, even if requirements for diagnostic confirmation are embedded into treatment eligibility guidelines. This scale of budget impact would likely present a barrier to patient access regardless of the understood efficacy and value of the new innovation. Further, as many of the costs associated with Alzheimer's disease are currently borne outside of the health system, there will be no short-term savings associated with new innovations to effectively offset their cost. Evidence of savings offsets may manifest over time, but current budgeting horizons of one-to-two years are inadequate to capture these potential long-term, broader economic and societal, cost-savings opportunities for individual payers, health and social care systems or societies as a whole.

THE OPPORTUNITY

Work with assessment bodies, payers, policymakers and industry to identify potential funding models tailored to the unique attributes of Alzheimer's disease

The ultimate goal in introducing new diagnostics and therapies for Alzheimer's disease is to provide access to patients who will benefit, while maintaining the overall sustainability and fiscal balance of the health system. To that end, initial efforts to ensure adequate funding for Alzheimer's innovations should focus on cushioning the budgetary impact of a sudden and significant increase in health spending, perhaps through conditional agreements providing access to interim funding, and by increasing the time horizon of budgetary evaluation to bring it closer into alignment with the longer time horizon of impact from Alzheimer's disease therapies. Ultimately, even an interim agreement would require additional financial resources from the health system, and this will require political will and the potential re-allocation of funding resources towards health expenditure. The feasibility of securing adequate political will and funding allocation for new Alzheimer's diagnostics and therapies would be increased by providing decision-makers with assurances that the value of innovations could be confirmed and re-assessed in practice. Further, payers should be included early on in any deliberations on articulating the benefits delivered by Alzheimer's innovations. Capturing diverse perspectives early in the process of developing new funding models will help to protect against the risk of perceptions of cost-effectiveness being adversely affected by models not capturing the full range of relevant therapy benefits.

Learning from the Cancer Drug Funds Experience

The Cancer Drugs Fund in the United Kingdom provides patients with access to cancer drugs that NICE deemed not cost-effective according to its standard criteria. Because of the Fund, NICE can recommend "managed access" for a set period during which funding is provided by the Cancer Drugs Fund and further real-world evidence is collected on patient outcomes. The experience has been a successful one for boosting patient access—following a re-evaluation of 33 drugs formerly supported by the Fund, 30 went on to be recommended for NHS implementation through conventional financing channels.

Source: Cancer Research UK. "The New Cancer Drug Fund Has Quietly Reached a Significant Milestone." December 2018. Link

THE CHALLENGE

Evidence on the long-term benefits of Alzheimer's disease innovations will be unavailable at launch

While the lack of long-term real-world evidence on the efficacy of new Alzheimer's diagnostics and therapies presents a major challenge to health technology assessment bodies and the models they have traditionally employed, it presents an equally meaningful barrier to funding. Given the importance of managing budget impact, access to new Alzheimer's disease innovations will be contingent upon both a favourable value assessment recommendation as well as a sustainable funding solution. While certain types of evidence can be generated pre-launch, other types of evidence will only become available once real-world patient cohorts are monitored over the decades-long time horizon associated with Alzheimer's disease progression. If stakeholder expectations for the timing of evidence generation are misaligned, the development of an infrastructure for filling post-evidentiary gaps would likely be delayed.

THE OPPORTUNITY

Use longitudinal real-world evidence to update access decisions

The uncertainty in clinical and economic impact and potential for real world data collection presents opportunities for more innovative adaptive access models that aim to "share the risk" from initial uncertainty of treatment benefit. In this model, additional evidence of benefits and reduced uncertainty feeds back dynamically to influence value assessment, pricing, and reimbursement practices, as well as allowing healthcare systems to refine the patient populations eligible for treatment. The Italian health system provides an example, with lessons for the introduction of Alzheimer's innovations: in Italy, a "payment by results" type model is used wherein disease registries track outcomes, with companies providing financial rebates depending on the clinical benefits actually delivered." [21]

"We need to find a system built on trust that allows for follow-up at multiple time points on all aspects of value—including efficacy, treatment population, diagnostic criteria, etc."

Reimbursement Leader, PIAdT Workshop, November 2018

WHAT DOES GOOD LOOK LIKE?

Core features of effective Alzheimer's innovation valuation

Traditional valuation assessments and data collection mechanisms are insufficient for unlocking access to new Alzheimer's disease innovations and safeguarding the promise of impact for patients and their carers. The effective valuation of Alzheimer's innovations will be underpinned by an enhanced understanding of the natural history of Alzheimer's disease and its early stages of progression, enabling assessment bodies to measure the impact of a new treatment or diagnostic against a credible baseline. The understanding of the disease's progression could be dynamically updated through the collection of longitudinal patient data after the launch of a new treatment, therapy, or diagnostic. The evidence collected through a standardized data infrastructure might also to be fed back to policymakers and regulators to influence assessment, pricing, and reimbursement practices in line with emerging evidence on the impact of innovative therapies. Further, an evidence collection infrastructure would also allow healthcare systems to refine patient populations eligible for treatment based on real-world data and experiences.

Policymakers and regulators could pair emerging evidence on the impact of new treatments or diagnostics with new value assessment models that include a consideration of the full range of societal benefits and cost-savings associated with innovative Alzheimer's treatments and diagnostics. Ultimately, the results of these impact assessments could be incorporated into financing models that respond to the complexities and unique challenges presented by Alzheimer's disease, along with its public health impact and the overall economic value of future innovations for society.

"Alzheimer's disease creates the opportunity to map the areas of impact that need to be considered for value assessment, rather than being strictly prescriptive about what health technology assessments should do."

Health Technology Assessment Leader, PIAdT Workshop, November 2018

THE WORK AHEAD:

Introducing PAVE

Project Alzheimer's Value Europe, or PAVE, will continue to develop the work started by the Pathways for the Introduction of Alzheimer's disease Treatments (PIAdT) Working Group that is catalogued in this report. Further, PAVE will leverage European-focused, and related work, including IMI's ROADMAP and others to develop solutions to the challenges related to value assessment of and funding for emerging Alzheimer's therapies and diagnostics. PAVE aspires to be a forum for increased collaboration and understanding between key stakeholders in the Alzheimer's ecosystem within Europe, including regulators, bodies responsible for health technology assessment, payers, clinicians, patient advocates, and industry members.

PAVE's goals are twofold:

1. To educate policymakers, payers, and other influencers in key European countries on the current challenges related to assessing value in Alzheimer's disease; and,
2. To work together with European payers and policymakers to develop solutions related to the value assessment of, and funding/financing for future Alzheimer's disease therapies and diagnostics.

In our first year, we will focus our efforts on generating an understanding of the evidence currently available for assessing value, and will gauge interest in innovative holistic value assessments for future Alzheimer's treatments and diagnostics. After this initial assessment period, PAVE intends to propose a framework for how modeling should be addressed, inclusive of key societal impacts of the disease. Finally, we will work to propose potential financing models that provide a realistic and enduring solution for ensuring that the incentives within the health system are aligned and reflect the public health impact and broader value of future Alzheimer's disease innovations for society.

PAVE

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Endnotes

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