The Value of Alzheimer's Disease Treatments and Diagnostics: An Industry Perspective

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EXECUTIVE SUMMARY

- There is a desperate need for new treatments to both address the unmet needs in the symptomatic treatment arena and modify the disease course, as well as diagnostic tools to identify target populations. To achieve this, innovation in drug development and holistic patient management needs to be systemically encouraged.

- For this to occur, treatments and diagnostics need to be appropriately valued.

- For Alzheimer's disease (AD), and particularly in the case of disease-modifying therapies (DMTs), demonstrating treatment value to a payer audience is challenging due to the differences between the positive impact that can be measured within registration trials and the longer term and broader benefits that are assumed to accrue to society. We need to be able demonstrate both individual and aggregate benefit of delaying or halting AD progression. Without changes to value recognition, these benefits will not be realized.

- We will need to garner stakeholder consensus to ensure that the broader and longer-term value and societal benefits of AD treatments and diagnostics are specifically considered in payer discussions. In line with this, we will need consensus regarding what data realistically should be expected at the time the first DMTs are available.

- A partnership between stakeholders is critical to further the move toward a value-driven health care system and advance solutions or focus on better frameworks to support value-based care decisions and address the affordability challenge.

INTRODUCTION

Globally, it is estimated that 47 million people worldwide suffer from dementia with an estimated cost of dementia care at US$818 billion in 2010. [1] By 2030 it is predicted that there will be 75 million people with dementia, and the cost of caring for these individuals could rise to around US$2 trillion.
In the US alone, an estimated 5.2 million individuals age 65 and older have Alzheimer's disease (AD) dementia - more than 10% of the population.[2] Cost of care for Americans age 65 and older with AD dementia and other dementias is $259 billion.[1] By 2025, the number of people age 65 and older with AD is estimated to reach 7.1 million - almost a 35 percent increase from 2017.[1]

Despite the immense impact of AD, there has been little advancement in its treatment over the past 10 to 15 years. Current treatment options are limited to five therapeutic agents. These existing treatments temporarily ameliorate memory and cognitive problems, and their clinical effect is modest; they do not treat the underlying cause of AD and do not slow disease progression.

Efforts to find treatments continue. Over the past decade, the focus of drug discovery and development efforts has shifted toward innovative treatments including new therapies to address the symptoms of AD and disease-modifying therapies (DMTs). The emphasis has also shifted to intervening early enough in the disease to maximally impact their effect on disease progression. As a result, new diagnostic tools are being developed with the intent of detecting pathology to confirm clinical diagnosis. This will be particularly important as DMTs become available.

For effective integration of approved diagnostic tool and future treatments into clinical practice, access will be critical. Making access decisions will require comprehensive assessment of value that takes into account the broad and immense impact and complexities of this disease to determine appropriate coverage and reimbursement. Although the payer and policy community understand the holistic benefit new therapies may offer, a key pragmatic concern is the likely high aggregate cost of an AD drug or diagnostic and how this will impact their affordability. Industry recognizes that this is a key concern to payers in particular and will collaborate to ensure financial sustainability of the healthcare system while ensuring patients and their families have access to treatments as needed.

The aim of this paper is to present an industry perspective on important considerations in determining value of AD treatments, as well as diagnostic tools, to guide access to the next generation of treatments and care paradigms.

DEFINING THE VALUE OF A TREATMENT IN GENERAL

With ongoing concerns about the rising costs of health care in general, health care service in the US is moving from a fee for service anchored to volume to one that is value driven. For health care systems that already consider value-based assessments, the evidentiary needs of the assessments continue to

become more stringent. Discussions around the value of any treatment and diagnostic need to similarly consider the full burden of a disease and how a treatment/diagnostic would reduce this burden.

The value of a treatment/diagnostic is a measure of the impact and benefits it brings in the context of its cost, over an appropriate time horizon. Assessing value should reflect the views of many stakeholders; however, regardless of the user, the core benefit should invariably be health improvement for the patient (enhanced or sustained prognosis, survival, independence, or quality of life).

Value assessment frameworks have recently been developed as a more encompassing path to assessing the worth of a treatment or diagnostic tool. These frameworks include various 'elements' (direct and indirect measures of drug effects). The specific elements included and their weight in the assessment is dependent upon the stakeholder(s) considered, in turn dependent upon the framework user.

Initiatives to define and measure the value of new and existing medicines have been and are being developed but have not been without their challenges. Methodologies have generally not been fully tested or validated, outputs are difficult to interpret, frameworks are disrupted if inputs are sub-optimal, there is a lack of a holistic viewpoint (i.e., beyond the direct drug effect), and focus is not always the patient. While the difficulties in adequately and comprehensively assessing all aspects of health care value from the perspective of all critical stakeholders are recognized, these value frameworks will likely be influential in determining what therapies are chosen by patients and health care professionals (HCPs), as well as if those therapies will be covered and reimbursed and made more broadly available to patients. There is opportunity for all stakeholders, including payers and industry, to collaborate on creating better frameworks to support patient-centered, value-based decisions.

DETERMINING THE VALUE OF AD TREATMENTS AND DIAGNOSTIC TOOLS

With the promise of innovative medicines for AD in the near future, discussion regarding value for AD treatment is coming to the forefront. The range of potential interventions and complexities of AD and the AD population challenge the current philosophy, structure and content of value frameworks for both treatments and diagnostics. Indeed, if decision makers apply current frameworks that exclude the holistic and societal benefits of the treatment to a DMT, there is risk of rejecting access to a potentially life-altering drug. Discussion around assessment of value should acknowledge the complexities and unique challenges of AD. Key considerations, also applicable to other disease states, are outline below.

Focus on Patient and Caregiver

Assessment of value requires effectively and appropriately balancing views, priorities and contributions of all key stakeholders (patients, caregivers, physicians, payers, innovators, health systems, and society overall). Regardless of the user, the core benefit in a value assessment should invariably be health improvement, or preservation, for the patient. The caregiver plays a pivotal role in the management of an individual with AD. A caregiver can recognize and communicate any impact of cognitive or functional

impairment on daily life (not always recognized by the affected individual), and also plays a central role in caring for the individual as disease progresses. Caregivers are also uniquely positioned to have an important role in treatment decision-making.

AD Implications: A central component of value should be ensuring a patient can maintain a sense of self and independence for as long possible. This will have substantial ripple effects beyond the patient. It is also essential to consider caregivers as central stakeholders in value assessment.

Embrace a Broader Perspective

Value assessment has generally been a one-size-fits-all approach focused on direct symptomatic benefit and common comparative metrics such as a short term medical cost-offsets calculation or cost-per-quality-adjusted-life-years evaluations. In the case of AD and other dementias, the effects of AD on the patient goes beyond the direct symptoms of the disease, and the burden of disease reaches well beyond the patient. Moreover, since the disease has no cure, effects are long term.

AD Implication: Benefits of an effective treatment or a diagnostic will resonate beyond the traditional boundaries of value assessment. Assessing value will require a system-wide long-term horizon perspective on value, beyond scales measuring cognition and function and likely beyond traditional randomized clinical trial methodologies.

A comprehensive view of value, centered on patient and caregiver, will need to consider the influence of a treatment or diagnostic on:

- Ability of affected individual to maintain independence (e.g. to manage own healthcare, to avoid/delay assisted living)
- Need for interrelated health care services, including physician visits, treatments such as drugs or surgeries, and hospital care as well as need for long-term care, support services and facilities.
- Burden to the caregiver
- Workforce productivity (both patient and caregiver)
- Quality of life, peace of mind, sense of self, sense of hope (both patient and caregiver)
- Management of co-morbidities and their broader life impact

The benefits of a broader view of value have been described for other diseases. For example, providing cochlear implants to children with severe hearing loss[3,4] results in greater social independence and more effective integration into mainstream education. The reduced dependence on special education support services results in a significant cost saving and, moreover, long-term potential for enhanced education and greater employment opportunities.

It is particularly challenging to assess the broader impact of potential AD treatments and diagnostics in the clinical trial environment and the full evidence of impact is unlikely to be adequately captured. Primary endpoints of clinical trials generally focus on narrow constructs of treatment benefit in an intended-use population and in the case of AD treatment trials, focus is on cognition and/or function as

measure of efficacy to satisfy regulatory requirements. Moreover, trials are designed to capture changes over relatively short time periods and, for a slow progressing disease like AD, this creates further challenges to demonstrating benefits that resonate with payers. These challenges can be mitigated to some degree by extrapolating the shorter term benefits of treatment to demonstrate the potential longer term impacts, though these extrapolations may have limitations.

AD Implications: In light of the uncertain timing and magnitude of the effects of treatment of treatment, real world evidence (RWE) and long-term modeling will be required to supplement the findings from clinical trials and help decision makers understand the broader context of a treatment/diagnostic innovation; engagement of patients and their caregivers in research design and endpoint selection will be essential. Decision makers will need to provide for access on less robust data than required in other disease areas. Requiring similar outcomes data to those from other disease states will prohibit the development of a DMT.

The broad reaching effects of AD on the patient, caregiver and society are such that one can expect diverse views on preferences and priorities of treatment needs.

AD Implication: Understanding preferences of the AD patient segment is critical. This need for tailoring and segmentation calls into question the all too common practice of assuming one model is appropriate for all patients. Value frameworks should be validated to ensure they actually reflect societal preferences with respect to AD decision-making.

As well as tailoring to patient needs, value assessment needs to be tailored to the treatment type. Future treatments will differ in their mechanism of action and thus appropriate efficacy measures and the point along the AD continuum at which they would be most beneficial will differ. Unlike symptomatic treatments, DMTs on the horizon will not improve symptoms, only potentially slow (or, ideally, stop) further disease progression, and early (preclinical, prodromal/MCI or mild AD dementia) treatment will be required to be effective. Moreover, DMTs will act to delay progression of the disease over the course of years rather than alleviate symptoms within weeks/months. No treatments in current development are curative.

AD Implications: It will be important to value and reward a relative reduction in patient decline and/or progression of the disease over time. A broader ecosystem needs to be in place for an effective DMT to deliver patient and societal benefits.

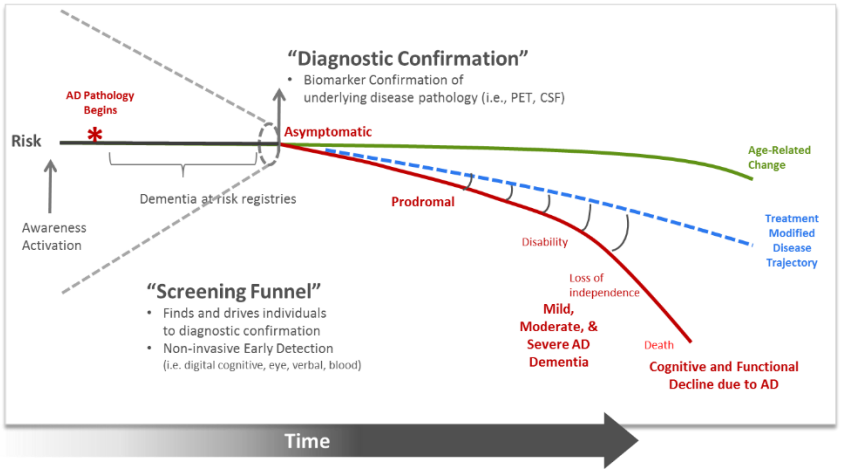
Support Early Diagnosis for Early Intervention

Current theories suggest that the onset of cognitive decline occurs 20 to 30 years after pathophysiological changes begin.[5] Additionally, diagnosis is generally made some time after cognitive decline starts, either in the prodromal AD stage or, in most cases, when dementia is already present.

AD Implication: Since there is no cure for AD and future treatments are aimed at limiting further decline, there is need to intervene early in the disease before significant harm has manifested. Development of broadly accessible advanced diagnostic tools can help support early diagnosis.

The importance of the right person getting the right drug at the right time cannot be overemphasized (FIGURE). To identify appropriate target populations for DMT use, diagnosis needs to occur early, either in the prodromal stage when symptoms are apparent, or earlier when affected individuals are still clinically asymptomatic. Diagnosis at the prodromal stage could be assisted by improved access to simple cognitive assessment tools in clinical practice, as well as structured methods for detection of cognitive decline in the Medicare Annual Wellness Visit (AWV). Recent Medicare changes, with the introduction of the G0505 code, will also be valuable for earlier diagnosis. To effectively diagnosis earlier, advanced imaging or biomarker diagnostic tools will be required.

FIGURE - Early diagnosis to change trajectory of disease (figure courtesy of Janssen diagnostics)



FOOTNOTE - Diagnosis may occur either during the asymptomatic or prodromal AD stage. The types of diagnostic algorithms appropriate for use in the asymptomatic and prodromal AD stages will likely be different, given anticipated differences in the sensitivity/specificity of detection tools and size of potential treatment populations at different disease stages.

While treatment options are currently limited, there is value in encouraging early diagnosis now:

- Earlier intervention, even with currently available non-pharmacological options, can slow cognitive decline.[6]
- While limited approved treatments are available, there are current opportunities to participate in clinical trials of experimental treatments for affected individuals and their families to explore.

Based on a search of clinicaltrials.gov, there are currently more than 100 Phase 2 or Phase 3 interventional AD studies recruiting participants. (search May 9 2017)

- Earlier diagnosis assists families with planning for future changes in living situation or financial responsibilities. Earlier diagnosis may also help limit potentially dangerous situations associated with cognitive or functional impairment. In a recent community study, for example, older adults with probable dementia who are not aware of a dementia diagnosis are more likely to report engaging in potentially unsafe behaviors including driving, preparing hot meals, managing finances and medications, attending doctor visits alone.[7]
- Comorbidities could be detected/anticipated and treated/planned for.
- Information collected from standardized screening could help provide a greater systematic understanding of cognitive decline on a population basis
- There is opportunity to lay the groundwork for future treatments. This is particularly relevant in the case of DMTs which, because they act to slow disease progression, may be more effective if used earlier in the disease continuum.
- For reasons outlined above, individuals want to know if they or a loved one is affected. In a recent survey of adults age 18 and older in USA and Europe, the Value of Knowing Survey,[8] over 85% of respondents said that if they were exhibiting confusion and memory loss, they would want to see a doctor to determine if the cause of the symptoms was AD. Over 94% would want the same if a family member were exhibiting the symptoms. Approximately two-thirds of respondents said that, they would get a medical test which would tell them whether they would get AD before they had symptoms.

Recognize Risk in Drug Development and the Importance of Innovation

AD is a complex disease and drug/diagnostic development and clinical development has been filled with setbacks. A recent review of AD trials on clinicaltrials.gov found that of 244 compounds studied in the decade 2002-2012, only one received regulatory approval, with an overall attrition rate of 99.6%.[9] With this high failure rate and the need for innovative treatments to overcome AD challenges, cost of AD drug development is immense. Industry recognizes the opportunity in the AD space and some companies have chosen to take on this risk and accompanying costs.

AD Implication: Ideally, any assessment of value in the AD space should also help encourage continued incremental advances in innovation akin to the progress made in oncology over the past few decades; that is, investment in and reward for development of innovative therapies and a continuing process of innovation is going to be key if innovation is to continue[10].

THE COST OF INNOVATION

Value depends upon the benefits of a treatment/diagnostic balanced against its cost, which encompasses the price of drug and other costs associated with its production and use. Coverage and reimbursement decisions depend not just on the value of a drug/diagnostic but also whether it is affordable. That is, does a health care system operating under tight budgets, or an individual patient, have the financial resources to prioritize payment for the drug/diagnostic?

In light of the immense challenges in AD drug development and potentially multi-faceted interventions as well as the anticipated high number of affected individuals, direct treatments costs will increase beyond those for the limited standard of care currently in place. Moreover, costs and benefits will occur at different times and across a variety of different payer systems (Medicare/Medicaid, public/private, US/international). As a result, payers will be required to go beyond a focus on the short-term budget impact to an appreciation of long-term measures of cost effectiveness to maximize the drugs' value for societal health.[11]

Industry can play a role in helping drugs be affordable, including offering discounts and ensuring that the appropriate target population (i.e., where highest value) is clear and identifiable. With increasing emphasis on value, there is opportunity to hold industry more accountable for delivering effective and targeted treatments in the real world care of payment. Value-based arrangement, where payment based on clinical or economic outcomes, encourages targeting of appropriate population and allows both parties to share risk. To advance in this direction, an environment that encourages health plan providers and drug developers to partner needs to be cultivated. In the case of AD where outcomes are longer term, a value-based arrangement will be challenging and will require collaboration between stakeholders to ensure appropriate data, including those of relevance to stopping rules, are made available to inform decisions.

ONGOING INITIATIVES AND COLLABORATIONS

To extend the definition and use of value frameworks to meet the highlighted challenges requires collaborations across clinical and outcomes experts from payers, academia, government, patient and caregiver organizations, and the pharmaceutical and diagnostic industries. Examples of ongoing initiatives are outlined below.

Real world outcomes across the AD spectrum for better care: Multi-modal data access platform (ROADMAP) - Innovative Medicines Initiative 2 (*IMI2).*[12]
IMI, a partnership between the European Union and the European pharmaceutical industry, seeks to facilitate collaboration between the key players involved in health care research to speed up the development of, and patient access to, innovative medicines, particularly in areas where there is an unmet medical or social need.[13] ROADMAP aims to create the conditions for an open collaboration

among stakeholders that yields consensual, efficient uses of a real world experience (RWE) platform for the ultimate benefit of AD patients and their caregivers across the spectrum of disease from preclinical AD through AD dementia. Briefly, ROADMAP plans to deliver a series of data integration methods and tools focused on patient outcomes and pertinent to value assessment. Methods and tools will be developed and tested through pilot projects, which are scalable and transferable, and will provide the foundation for a future Europe-wide RWE platform on AD.

Project Insight

Launched by Global CEO Initiative on AD (CEOi) in 2015, this partnership between industry, US public and private payers and health care systems is focused on improving disease prediction as well as measuring disease burden and modeling treatment effect. The first phase of research aims to create a claims-based predictive algorithm using US Medicare data, with initial release in spring of 2017. Additionally, starting in 2017, Project Insight aims to model the benefits of future treatments, using cluster analysis to identify existing cohorts of dementia subtypes based on cost and utilization patterns, and explore the US commercial payer and Medicare health care costs for these clusters, with the goal of estimating cost impacts of improvement in dementia.

Green Park Collaborative[14]

This collaborative will foster a shared understanding between industry, health systems, and other key stakeholders regarding current scientific innovation in AD drug development and the challenges that arise in demonstrating patient benefit and value for health plans. The aim is to develop a consensus set of recommendations for assessing value of new AD drugs that will be stakeholder informed, and balance efficiency, rigor, and timeliness of studies against the need for results that are meaningful to patients, providers, caregivers, and payers.

CEOi Duke-Margolis Center for Health Policy meeting (June 2017): Developing a path to enhance the quality of care for AD patients

Key stakeholders, including payers, providers, drug manufacturers, patients, and caregivers, will convene to discuss and align on principles that categorize valuable outcomes at all stages of AD, and identify payment approaches that could be used to reward novel AD therapies.

Gerontological Society of America (GSA) Partnerships ***Workgroup on Cognitive Impairment Detection and Earlier Diagnosis*** [15]

The 2010 Affordable Care Act established the AWV as an opportunity for Medicare beneficiaries to receive preventive and assessment services during visits with their primary care providers. While detection of cognitive impairment is among required AWV services, no specific tools are mandated and no data are available regarding tools used for this purpose. A team of experts, including those from the Alzheimer's Association, assembled by GSA (the Workgroup on Cognitive Impairment Detection and Earlier Diagnosis) will collaborate to review available evidence-based cognitive impairment detection tools for use by primary care providers, and recommend how more uniform detection can be adopted nationally via the AWV. The ultimate goal is to establish earlier detection and improved diagnostic

methods as well as links for post-diagnosis support services to benefit individuals with dementia and their families.

Alzheimer's Disease - Patient and Caregiver Engagement (AD PACE)

This patient and caregiver led consortium is supported by industry and NGO's and targeted at developing a sustained platform for the development of patient/caregiver-focused insights and preferences across the disease spectrum and the wide range of heterogeneous sub-populations experiencing this disease. A program of qualitative and quantitative studies is being developed to ensure a person-centred approach to drug development as well as regulatory and payer decision making.

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