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Modelling the value of innovative treatments for Alzheimer's disease in the United States

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ABSTRACT

Alzheimer's disease (AD) is the predominant cause of dementia and a leading cause of death globally. With no cure or treatment to slow disease progression, AD-related healthcare costs are substantial and increase as the severity of the disease progresses. Given the complexity of this disease, including initial pathophysiological damage occurring decades before clinical manifestation, finding new impactful treatments for AD relies on highly innovative research and development. However, such sizable and sustained investments bring into question whether conventional value assessment models are fit for this purpose. In this article, we examine the importance and challenges of assimilating the perspectives of varied stakeholders, including patients, caregivers, health systems, payers, and society at large, into a comprehensive value assessment model that may be well suited for a breakthrough treatment for AD.

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Introduction

Dementia refers to a group of symptoms, including difficulties with memory, language, and cognitive skills, that affect a person's ability to perform daily activities. Alzheimer's disease (AD) is estimated to represent 60–80% of all dementia cases¹. Symptoms in AD progress gradually from a baseline of normal cognition to dementia². There is no treatment currently that prevents, cures, or slows the progression of AD; current medications are indicated for the symptomatic treatment of mild to moderately severe AD dementia, ameliorating symptoms such as cognitive and functional decline, for a limited time³. Current symptomatic therapies available in the United States include cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) and memantine, an N-methyl-D-aspartate receptor antagonist⁴. In addition, a memantine and donepezil combination therapy is approved in the United States⁴. Despite the availability of symptomatic treatments, AD remains both progressive and irreversible, making it one of the leading causes of death globally⁵. Of the top 10 causes of death in the United States in 2017⁶, AD is the only one for which there is no current treatment option to slow disease progression by addressing the underlying disease pathology⁷. Even in the absence of a disease-modifying therapy, early diagnosis of AD is important to allow patients and families time to access life-planning advice, financial support, and nonpharmacological and pharmacological treatments⁸. Early diagnosis and intervention may lead to higher up-front

costs, which may be offset by subsequent savings, primarily in institutionalization costs⁹.

AD-related costs increase as a patient's cognitive and functional skills decline¹⁰, which leads to greater dependence on the long-term care system, informal caregivers, and social care¹. Patients with AD and their families pay a substantial amount for out-of-pocket care-related costs. A retrospective cohort study of data collected between 2005 and 2010 in the United States¹¹ found that the average out-of-pocket spending for patients with dementia was 81% higher (\$61,522) than spending for patients without dementia (\$34,068). Data collected between 2004 and 2015 in the Health and Retirement study revealed that cumulatively over the last seven years of life, a higher burden of healthcare costs was attributed to families of patients with dementia compared with families of patients without dementia¹². While these known informal caregiving and out-of-pocket costs are significant, a large proportion of the true societal costs are likely hidden¹³.

The impacts of AD to patients and their families are tremendous and go well beyond the direct financial costs¹⁴. Only 16% of AD costs are directly paid for by the healthcare system, with the vast majority of this enormous cost burden borne by the patient/caregiver in the form of social care costs (42.3%) and informal care or indirect costs (41.7%)¹⁵. Given the significant unmet needs for this population and burdensome societal impacts, there is a keen interest in

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expanding the therapeutic arsenal. Novel therapeutic approaches aim to slow AD progression by addressing the underlying pathology of the disease, which can appear as early as 20 years prior to clinical manifestation¹⁶. The launch of such therapies would represent a transformative change for patients with AD.

As AD impacts many factors pertinent to families and society at large, traditional methods for performing value assessments, while useful, may omit some important value considerations. The question then naturally arises how to value therapies that will impact not only the future course of medical spending but aspects outside of direct medical spending, such as social care factors and costs, caregiver or family burden, quality of life, and related impacts of the disease.

What follows is a discussion of key valuation issues facing a breakthrough AD therapy—from the perspectives of patients, patient advocates, payers, policy makers, health economists, innovative manufacturers, and society at large. The discussion here builds upon the themes raised in a session at the virtual ISPOR (International Society for Pharmacoeconomics and Outcomes Research) 2020 Symposium.

The importance of encouraging innovation

Payers and health systems face the challenge of ensuring patient access to new therapies while concomitantly rewarding effective innovation and serving as judicious stewards of limited financial resources. A thoughtful and balanced approach is needed to ensure that while patients have equitable access to these effective new treatments, manufacturers are incentivized to develop new therapies over the long term. The challenge to manufacturers is embodied by the history of failure and associated financial risks of investing in uncharted therapeutic areas. These desires create an inherent tension—how to support the consumer's need for lower prices and expanded use while enabling the innovator to make significant investments in research and development (R&D)¹⁷.

The interest in providing incentives for innovation is recognized worldwide. According to some estimates, in 2018, the US federal government covered approximately 22.2% of R&D expenses, while pharmaceutical companies covered 66.7%¹⁸. Policy makers recognize the risky nature of innovation and hence have developed incentives to encourage R&D to find treatments for diseases and reach patient populations that would otherwise be neglected. The introduction of the 1983 US Orphan Drug Act, for example, increased the development of treatments for rare diseases¹⁹. In addition, the implementation of Medicare Part D both improved prescription drug coverage for older patients, and further resulted in an expansion in the number of clinical trials in diseases affecting this population²⁰.

Innovation is inherently risky, and the way that regulators and payers measure the value of innovation is vital to the fair and comprehensive assessment of an innovative treatment. Thus, an additional avenue to recognize the value of innovation is to expand the types of meaningful benefits

included in value assessment. Currently, there is a lack of innovative treatments for AD. However, the way the value of the first breakthrough treatment (e.g. one that treats the underlying pathology of AD) is assessed will set the course for future innovative therapies.

Challenges with value assessments

Multifaceted value of innovative therapies

Current value assessments often evaluate the overall (incremental) costs per quality-adjusted life year (QALY) to determine if the result is “cost effective”, as benchmarked against the value of the QALY. This framework of value allows payers to assess the value that new treatments bring to the health system²¹. Such analyses provide a tool that allows payers to compare the effectiveness of interventions across disease areas to make decisions on resource allocation²². However, many published cost-per-QALY analyses do not generally recognize the burden of disease on family, caregivers and society and therefore do not fully recognize the value of treatments that may help alleviate that burden. Typical cost-effectiveness frameworks include direct patient costs and benefits only and omit the numerous opportunity costs. Furthermore, for a disease such as AD in which the patient becomes dependent on caregiving for everyday functioning, the caregiver is effectively considered a dyad with the patient—their lives are commingled. From this perspective, the impact of disease on the caregiver is critical to include in the evaluation. Thus, value assessment frameworks should become more AD-patient centric and evolve to better reflect long-term health. Furthermore, the frameworks must be adapted to capture the burden of disease on families, caregivers, employers, and society.

Various entities are striving to identify a more comprehensive approach to value assessments. For instance, the ISPOR Special Task Force value “flower”²¹ (Figure 1) is a framework that incorporates the core elements of value assessments (QALYs gained and net costs), as well as elements inconsistently used in value assessments (productivity and adherence-improving factors), and potential novel value elements not typically captured (reduction in uncertainty, fear of contagion, insurance value, severity of disease, value of hope, real option-value, equity, and scientific spillovers). This framework moves beyond conventional cost-per-QALY analyses and outlines a more comprehensive approach to value assessments that may better capture the broader value that an innovative therapy may bring to society.

Two of the novel elements of the ISPOR Task Force's value “flower” are the real option-value and the value of hope. Real option-value refers to the value created by a health technology that extends life and creates opportunities for the patient to benefit from other future advances in medicine²³. Hypothetically, if patients had to choose between two interventions offering the same expected QALY gain, they may prefer the intervention that provides a greater chance to benefit from access to future scientific and clinical advances²¹ (although the potential costs of those future advances should also be taken into account). The value of hope refers

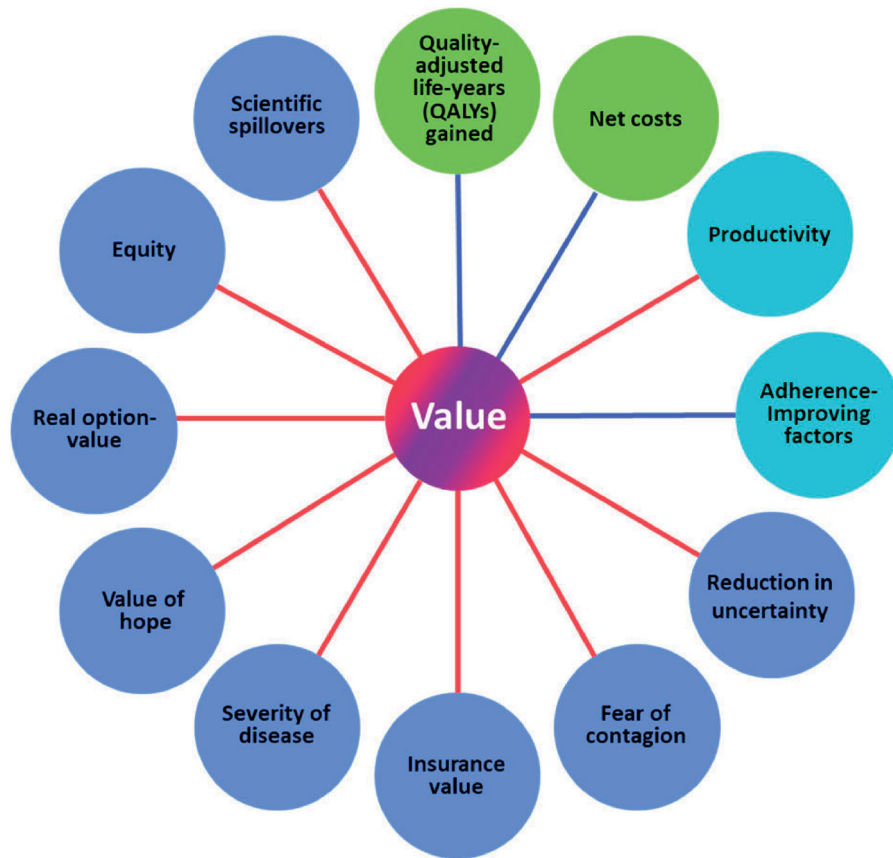


Figure 1. Elements of value as a framework for value assessment. Circles represent core elements of value (green), common but inconsistently used elements of value (light blue), and potential novel elements of value (dark blue). Lines represent value element included in traditional payer or health plan perspective (blue) and value element also included in societal perspective (red). Reprinted from Lakdawalla DN, et al. *Value Health*. 2018;21(2):131–139, Copyright 2018, with permission from Elsevier.

to the fact that patients may be more willing to take chances on therapies that offer small probabilities of larger gains, rather than focusing solely on the mean gains in QALYs. Many severely ill patients, for example, may be willing to trade off some survival (e.g. undertaking a risky procedure) for the chance of a “cure”²¹, even if there is a very small probability of success.

The value “flower” approach is in line with traditional recommendations from consensus groups²⁴, which suggest that cost-per-QALY analyses should be integrated with other considerations such as affordability, budget impact, fairness, feasibility, and any other criteria deemed important in local settings. In addition, the perspective of all relevant stakeholders—patients, caregivers, clinical experts, health system administrators, and society in general—should be considered in the assessment. However, one should recognize that if we build other elements into the QALY, the cost-per-QALY threshold may need adjusting downward because the value of a QALY would have changed. In other words, we need to reconsider what resources society is willing to forego to obtain the “new” QALY. Society’s preference for equity in opportunity to benefit from treatment suggests that more value is placed on innovation where no current therapy exists; this is the case in treatments for rare diseases²⁵ and is also true for future therapies that target the underlying

pathology of AD. According to the Second Panel on Cost Effectiveness in Health and Medicine, cost-effectiveness analyses should include an “Impact Inventory” that presents healthcare system and societal perspectives in distinct reference cases²⁶.

A quantum leap in innovation in treatment for a disease may be valued more than incremental steps that, over time, achieve the same aims. However, in an area of rapid innovation and R&D investment, a new therapy that advances the scientific field can contribute significantly, even when “scientific spillovers” are not considered part of value assessments. Highly active antiretroviral therapy (HAART) for HIV is perhaps the canonical example. In the years prior to HAART’s introduction, AIDS remained one of the most devastating diseases globally with a significant unmet need. The entry of HAART in 1995 significantly improved patient survival; it was estimated that life expectancy for individuals with AIDS was 3 years in 1984, compared with 16.5 years in 2000²⁷. However, HAART was introduced with prices higher than the estimated value. Ultimately, long-term research demonstrated that new drugs to treat HIV/AIDS, including HAART, that first came on the market in the late 1980s dramatically improved survival, which was valued at more than \$1 trillion in overall value, with 5% of this distributed among the manufacturers²⁷.

Challenges of applying current value assessment frameworks to new AD therapies

We focus on three questions regarding challenges in the methods and process of value assessments for AD therapies.

Do QALYs undervalue treatments for older patients?

Some cost-per-QALY analyses have reported more favorable cost-effectiveness for interventions targeted to older versus younger populations because the former have higher disease prevalence or more risk factors and, ultimately, more to gain from successful therapies²⁸. Still, given that older people have a lower remaining life expectancy than younger people, interventions for older people may produce less QALY gain than interventions for younger populations²⁹. In light of this, and recognizing that approximately 80% of people with AD are >75 years old¹ with an estimated mortality rate that is higher than that of a younger population, the use of the cost-per-QALY methodology raises important ethical questions about how to allocate resources for interventions affecting mostly older populations with potentially multiple comorbidities²⁹. Additionally, in 2014, of individuals with AD or a related dementia who were ≥ 65 years old, one in five to as many as one in three had coexisting conditions such as congestive heart failure, chronic kidney disease, diabetes, or coronary artery disease¹. Interventions for severe conditions such as AD may also warrant special consideration, e.g. higher cost-effectiveness benchmarks to address the cost-per-QALY limitations relevant to AD³⁰.

Non-QALY metrics can also be presented alongside QALYs. An overarching goal in value/health technology assessment is to assess clinical evidence, costs, and societal and ethical impacts in structured and standardized ways. Value/health technology assessment should be transparent and include high-quality data on aspects of care and outcomes that are important to patients and other stakeholders whenever such data exist. Researchers, value assessors, and the patient community agree that conventional approaches to value assessment often inadequately account for the many dimensions of value.

Should cost-effectiveness analyses capture a societal perspective and account for savings beyond healthcare-related costs?

Capturing value beyond the health system is critical for appropriately measuring the value of all innovations, including public health programs, diagnostics, and procedures, as well as drug therapies, such as those for AD. Direct healthcare costs form a relatively small proportion of the known costs of AD, and many value assessments exclude non-healthcare-related costs. In a study published in 2013, informal care costs for dementia were projected to rise to \$255 billion in 2020 (in 2010 USD)³¹, and this finding may have missed "hidden" costs (e.g. those due to delays in diagnosis). Another study found that 70% of cost-utility analyses for AD and other dementias considered at least some family or caregiver spillover costs, but only 19% considered spillover

health effects³². A recent literature review of multinational studies found that informal care costs represent approximately 60% of total costs for patients with early stages of AD, increasing to 72.5% for patients with severe AD³³. Although cognitive decline has been identified as the main driver of societal costs of patients with AD³⁴, both cognitive decline and physical disability were found to be predictors of increased informal care costs³⁵. Moreover, the need for social and informal care is already higher in patients with mild cognitive impairment likely due to AD than age-matched controls and increasing further in patients with AD dementia³³. The providers of informal care are also an important element to consider for cost-effectiveness analyses, as it is estimated that an intervention may no longer be considered cost effective if professional care replaces caregiving by family members³⁶.

Medicare pays for medical care and only some short-term supportive care. However, low Medicare costs for AD does not mean low health system costs. Medicaid, a secondary payer for people with Medicare, is an important source of funding for AD care. Medicaid pays for most of US nursing home care costs, and in 2014, >60% of nursing home residents had moderate to severe dementia¹. Most states have waivers that expand coverage to home and community-based services and support for Medicaid beneficiaries who are at risk of needing nursing home care. Medicaid also pays the Medicare Part B and Part D premiums and may pay the Medicare cost sharing for dual-eligible beneficiaries.

Medicare by statute would cover effective therapies for individuals that prevent or delay AD and dementia. However, Medicaid, as the primary payer of long-term services and support, such as custodial care in nursing homes and home care programs, is the government program that would benefit the most from disease-modifying therapies. The adverse consequences of poor integration of Medicare and Medicaid have been a long-standing concern³⁷.

Furthermore, patients with AD generally have multiple comorbidities^{1,38}, which can exacerbate the disease and increase care requirements. Caregivers report higher levels of stress and emotional difficulties¹, due to the increasing requirements of patients with AD, which in turn can increase the caregivers' susceptibility to health complications and impact their work opportunities and productivity. Collecting evidence on the possible treatment effects on such broader costs and benefits, and reflecting them in cost-effectiveness analyses, is important because it will likely influence results. Additionally, measures of productivity should be broadened to include productivity that is not traditionally economic. Without addressing these limitations, valuations of breakthrough therapies in AD may be too low.

How can we best capture the value that an AD therapy may bring to society?

The health and quality-of-life impacts of AD are typically captured by proxy respondents, such as caregivers, due to the reduced cognitive ability of the patient. Caregivers are often family members providing informal care until a greater loss of independence leads to formal social care and

institutionalization. Therefore, value assessment approaches should consider the input of all stakeholders at the appropriate steps. A wide range of criteria needs to be considered in a holistic way to ensure meaningful insight into the broad impact of AD and the value that an innovation may bring to patients, caregivers, and society at large. Integration of behavioral economics would add the perspective of those actually living with AD and their family caregivers, instead of only healthy consumers or economists who are merely contemplating what living with AD might be like and then making assumptions about what matters to those who have the disease. Furthermore, value assessments should explore the heterogeneity of effects within a patient population³⁹. For instance, patients and caregivers may have divergent preferences regarding health outcomes and different interventions, which should be investigated.

Recommendations and conclusions

To enable a wider range of value elements to be incorporated into the value assessment, additional data will be required, such as improved data on the disease natural history, costs, and utilities; comorbidities associated with the disease; and societal impact of the disease. This will require consideration of the perspectives of all relevant stakeholders, including patients, caregivers, clinical experts, health system administrators, economists, and policy makers. Simultaneously, value assessments should embrace the collection of real-world evidence to address any incomplete information or any uncertainties, particularly for disease natural history prior to and following diagnosis.

Value assessment should use robust methods and models that can integrate a broader set of value elements. This may require adapting existing models or creating new models to explore the value of a breakthrough. For some diseases, such as AD and other dementias, it would be beneficial if the model starts earlier in the patient's life (prior to diagnosis) to capture a better representation of the costs and utilities associated with the disease. A variety of techniques and data approaches should be investigated, such as multicriteria decision analysis, patient surveys, and Delphi consensus to capture patient preferences. These methods need to be adaptable to therapeutic advances, evidence standards, societal values, and evolving structure of health systems.

The first approved treatment that slows AD progression will represent a breakthrough step in innovation. Payers' and health systems' ability to assess value appropriately for this new treatment will influence future innovation not only in AD but also in other therapy areas. Many healthy individuals paying into the health system today may benefit from innovation in AD as it may address their or their families' future health needs; thus, it is in society's interest to continue innovation to progress toward a cure for AD. Better alignment of system-wide incentives with the societal willingness to pay for innovation in AD is needed, along with creative contracting and cost-sharing reforms. Such reforms are needed at multiple levels to address drug pricing and total costs of health care more broadly and extend to societal

costs as well as savings. Accounting for societal benefits and considering information alongside traditional cost-effectiveness analyses will be useful to appropriately value a breakthrough therapy in AD.

Transparency

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Author contributions

All authors contributed to the conception of this work and participated in the drafting and critical review of this article. They have provided approval of the final version to be published.

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