

MILLIMAN REPORT

Assessing the Value of Therapies in Alzheimer's Disease

Considerations to create a practical approach to value

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Executive Summary

The impact of Alzheimer's disease (AD) on caregivers, communities, and social service needs is profoundly larger than its impact on direct medical costs, as shown through financial and public health data. These impacts are interwoven with socioeconomic and racial disparities for patients and caregivers. Traditional value assessment models fail to fully consider the full scope of value for AD treatment. This observation is not new, but has been raised by many others.¹⁻⁴ In light of upcoming clinical development review and value assessment of several AD therapies, the Alliance for Aging Research engaged consultants from Milliman to develop a framework of useful principles for valuing the burden of AD and potential treatments. Although this report is not quantitative, it identifies how notions of value could be quantified.

AD has particularly far-reaching economic and societal effects, so any framework employed to assess the value of AD treatment should examine a very broad landscape to understand the burdens that exist and can be affected. Diseases vary in how they impact patients and society. Some conditions have relatively well-defined and short-term burdens and care costs that are dominated by medical expenses, such as hip joint failure and arthroplasty. Other conditions, including AD, have wide-ranging burdens and require large amounts of care that may not appear in accounting data. A value methodology that focuses on direct medical care costs may produce reasonable results for situations where outcomes are clear and strongly linked to medical spending. However, such a methodology will miss or undercounting indirect costs such as family caregiver burden and the societal harms of disparities for conditions such as AD.⁵

An equitable value assessment framework for use in AD should account for the ecosystem that surrounds people with AD, including the impact treatments may have on ameliorating social ills such as racial disparities. In particular, the framework should, a) utilize metrics that, when appropriate, apply the same standards regardless of age or socioeconomic status, b) capture the health-related value of AD treatments not only for patients but also for their family caregivers, and c) appropriately account for changes in non-health outcomes and issues of community value related to AD patients and their caregivers.

This approach represents an evolution from traditional methods used to determine the value of therapies. Traditional approaches generally rely on some calculation of cost effectiveness using monetary amounts divided by metrics for quality, where quality metrics capture patients' perceived outcomes (such as health state preference values), while monetary amounts are typically the direct medical costs associated with care for an average patient of interest. Sometimes assessments using traditional approaches are comparative (e.g., a therapeutic added-value approach) and contrast different treatment options to gauge the relative value of each.^{6,7} These methods have limitations when dealing with complex diseases, as they anchor on healthcare spending and outcomes for the directly affected patient alone and do not recognize value driven by public health improvement, transformation, or even societal value.

It is important to consider that the principles of value described in this report do not define to whom the value of therapy should accrue. There is certainly a wide range of views on this topic. To some, a substantial portion of the value belongs to the public, because the infrastructure to

research, develop, disseminate, and pay for therapy relies on society. To others, the value belongs to the innovators or investors who endured risk over years to bring a therapy to the market that can use it. The failure to separate assessment of value from the question of ownership means that payers view the determination of “value” as a cost to them, while the promoters of innovation view that value as revenue—and the issues of value become confused with financial interests. Separating the definition of who owns the value from the quantification of the value itself can help bring clarity to complex issues such as how to think about spending on AD patients. This report does not address in any way “to whom the value belongs.”

An influential stakeholder using the traditional approaches to value assessment is the Institute for Clinical and Economic Review (ICER), a non-profit organization that uses cost effectiveness to assess therapeutic value from a payer’s perspective. This report uses examples from a variety of ICER’s works across therapies as a basis for illustrating approaches for assessing the value of treatments for AD more broadly. The status quo of AD care consists of systems of care that depend on low-paid workers or family caregivers, create multi-generational family burdens, and exacerbate existing racial, ethnic, and socio-economic disparities. Although practitioners using traditional approach make some effort to capture non-medical spending and have recently acknowledged racial and ethnic disparities, these methods do not account for the value of treatment when the vast majority of a disease’s impact is on a family or community.

In addition, there are several technical issues that render the traditional approach problematic. These issues are not unique to AD, although the characteristics of AD and the ecology of care around people with AD highlight these issues.

The Alliance for Aging Research commissioned Milliman to develop an alternative approach to assessing value in AD and to explain weaknesses in the traditional approach. The Alliance is a Washington, DC-based non-profit focused on accelerating the pace of scientific research and advances that improve the experience of aging. Funding for this report was provided by the Alliance, which received supplementary grants from Biogen and from Eli Lilly and Company. This work reflects the view of the authors, who are employees of Milliman, which does not endorse any product or program. Bruce Pyenson is a Member of the American Academy of Actuaries and meets its qualifications for this work.

Alzheimer's Disease Overview

Alzheimer's disease (AD) is a degenerative neurological condition that progressively destroys patients' memory, language, physical function, and autonomy, driving escalating care costs and dependence on family caregivers. As of 2019, 5.7 million adults, most age 65 or older, were estimated to be living with AD in the United States (US).⁸ Over time, people with AD often require substantial nursing care, home and hospice care, as well as significant family caregiving and support.⁹ Total care costs for the management of AD were estimated at \$305 billion in 2020. However, this figure is likely understated due to insufficient measurements of informal care costs and caregiver health burden.¹⁰ Trends suggest these costs could increase to more than \$1 trillion as the US population ages.¹⁰

AD prevalence increases dramatically with age, and disproportionately affects women and minorities. While only 3% of adults age 65-74 have AD, 17% of those age 75-84 and 32% age 85 and older are affected.⁹ People younger than 65 can also develop AD, but it is much less common, and prevalence is uncertain. Of those identified with AD, nearly two-thirds are women, and studies suggest there may be an association between menopausal changes and preclinical AD symptomatology.¹¹ Some racial and ethnic minority groups also have greater prevalence of AD in addition to an earlier age of onset.⁸ According to the National Institute on Aging (NIA), older Black/African Americans and Hispanics/Latinos are disproportionately affected by AD and other dementias in comparison to older whites. Genetic factors do not account for these differences. Rather, health conditions such as cardiovascular disease and diabetes, which are associated with increased AD risk, may be to blame as they are more prevalent in Black/African American and Hispanic/Latino populations.⁸ People over age 55 with low income, less education, or who live in rural areas have also been linked to greater incidence of AD.¹² Studies show an association between a higher level of education and better brain health. For example, among adults aged 45 years or older, the proportion experiencing subjective cognitive decline was lowest for college graduates and nearly three times greater for those without a high school diploma.¹³ Individuals with at least nine years of education have also been shown to experience a delay in cognitive decline and a reduced period of dementia morbidity compared to those with fewer than nine years of education.¹⁴

AD is a leading cause of disability and poor health as patients can endure years of reduced function and independence as the disease progresses.⁹ Although generally thought of as a disease of old age due to patients' average age at first diagnosis, clinical manifestations of AD are thought to begin 20 or more years before symptoms arise.⁹ Characteristic symptoms of this disease, such as memory loss, mood and behavioral changes, language impairment, and diminished problem-solving capacity, advance over time and gradually impede patients' day-to-day lives. This decline in function is broken down into three general stages – mild, moderate, and severe – which reflect the degree to which symptoms interfere with one's ability to carry out everyday activities.⁹ Ultimately, this decline in function contributes to patient mortality. According to the CDC, AD is the sixth-leading cause of death in the US and the fifth-leading cause of death for those age 65 or older.⁹ Using the Global Burden of Disease approach, which is a

systematic way of quantifying the comparative magnitude of health loss due to diseases, AD climbs to the 4th leading cause of death.¹⁵

For some patients, mild cognitive impairment (MCI) is a precursor to AD and represents a transitional state between normal aging and dementia, but not all patients with MCI convert to AD.¹⁶ Diagnostics to identify patients with MCI and those most likely to progress to AD have become a central focus of research in the AD space.¹⁷ Researchers have found that even given higher functioning among patients with MCI, patients' cognitive impairment is significant enough to demonstrate a tangible impact on caregivers.¹⁸ This potentially complicated patient journey of AD patients, which may begin with MCI, poses one challenge to the definition of value for AD.

AD is linked to significant direct care costs, which makes its steadily increasing prevalence an economic as well as a societal concern. Patients with dementia are associated with average lifetime care costs from time of diagnosis of \$357,297 (in 2019 dollars).⁹ Of that cost burden, families are estimated to bear 70%, while Medicaid and Medicare bear only 14% and 16%, respectively.¹⁹ Medicare spends an additional \$2,101 (Parts A and B, in 2015 dollars) per year per beneficiary with AD on average compared to overall average spending of about \$10,000 per year, but Medicare spending for beneficiaries with AD actually declines in the year preceding death.²⁰

Unlike many other chronic diseases, a substantial portion of the healthcare costs associated with people with AD is not driven by medical procedures or inpatient care. Rather, 49% of total direct costs of AD are related to long-term residential nursing home care. Community-dwelling patients with AD experience 44% higher total annual medical and care expenditures than similar patients without AD. Expenditures have been observed to increase as patients' conditions deteriorate and 24-hour assistance with activities of daily living becomes necessary. For example, average Medicaid spending for patients with AD in the five years prior to death was eight times higher than for patients without AD.²¹ Because Medicare does not cover long-term care services, many patients must rely on Medicaid to cover long-term care costs. In one study, researchers found that 93% of incremental Medicaid expenditures associated with AD were for nursing home stays.²¹

Studies have consistently shown that active management of AD can improve the quality of life (QOL) of affected individuals and their caregivers.⁹ Unfortunately, there are no AD treatments currently on the market that permanently slow or stop the damage that causes symptoms.⁹ The five Food and Drug Administration (FDA)-approved drugs — rivastigmine, galantamine, donepezil, memantine, and a combination treatment composed of both memantine and donepezil — improve patients' cognitive symptoms, but the efficacy of these drugs is specific to the patient and results are temporary.⁹ Moreover, no drugs have been specifically approved to treat behavioral and psychiatric symptoms of AD. This contributes to the high rate of institutionalization among AD patients, as challenges with managing the severity of progressing behavioral symptoms (e.g., neuropsychiatric symptoms) have been reported as a primary precipitating factor for family members' choosing institutional care for their loved ones.²²

In the absence of preventive, ameliorative, or curative medical solutions, AD burden is expected to grow over the next 30 years.⁹ According to a study from the Rush Institute for Healthy Aging, the number of people age 65 and older living with AD is projected to reach 8.4 million by 2030 (a 45% jump from 2020) and 13.8 million by 2050 (a 138% increase from 2020).²³ Thus, it is both a societal and an economic imperative to identify cost-effective treatments and solutions that can help contain this growing burden of disease. However, current healthcare value assessment frameworks are not designed to comprehensively capture the value delivered by AD interventions. We propose the use of an integrated community health-oriented assessment framework or, in the absence of this alternative approach, suggest elements of traditional value assessment frameworks that must be addressed to determine treatment value more accurately in the context of a disease like AD.

Principles to Assess Value in Alzheimer's Disease and Dementia

Financial and public health data show that AD's impacts on caregivers, communities, and social service needs are profoundly larger than its impacts on direct medical costs. These impacts are interwoven with socio-economic, racial, and ethnic disparities in patients and caregivers. Given these far-reaching economic and societal effects, any framework employed to assess the value of AD treatment must examine a broad landscape to fully reflect the burdens that exist and can be affected.

Diseases vary in how they impact patients and society. Some conditions have relatively well-defined, short-term burdens and care costs that are usually dominated by medical expenses, such as osteoarthritic hip joint pain followed by elective arthroplasty. Other conditions, like AD, have wide-ranging burdens and require large amounts of care that may not appear in accounting data. A value methodology that focuses on direct medical care costs may produce reasonable results for situations where outcomes are clear and strongly linked to medical spending. However, such a methodology will overlook items such as family caregiver burden and the societal harms of disparities for conditions such as AD and may not capture patients or caregivers' caring about factors beyond survival and clinical measures of disease progression. This is especially true when valuing AD treatments, as their worth is likely to be underestimated without consideration of spillover costs, community-level consequences, and health effects related to caregiving.²⁴

For the above reasons, an equitable value assessment framework for use in AD should account for the ecosystem that surrounds people with AD, including the impact treatments may have on ameliorating social ills such as racial and ethnic disparities. In particular, the framework should:

- a) Utilize metrics that, when appropriate, apply the same outcomes standards regardless of age or socioeconomics,
- b) Capture the health-related value of AD treatments not only for patients but also for their family caregivers, and

- c) Appropriately account for changes in non-health outcomes for AD patients, their caregivers, and their communities.

UTILIZE METRICS THAT APPLY THE SAME OUTCOMES STANDARDS REGARDLESS OF AGE OR SOCIOECONOMICS

The metric that underpins the traditional value assessment framework is the quality-adjusted life year (QALY). Both ethical and quantitative critiques have been levied against the QALY, noting that its fundamental calculus is ageist, ableist, and unable to account for diversity of patient experience.^{25–28} Given that AD is a largely a disease of older age, which is characterized by reduced function over time, the QALY is a problematic metric for valuing treatment of AD.

It is notable that the Medicare Payment Advisory Commission (MedPAC), in assessing payments for quality improvement, has adopted the principle that while payment should be adjusted to account for socioeconomic differences, the quality measures themselves should not reflect socioeconomics because doing so can mask poor performance.²⁹ For example, the outcomes for a provider serving lower- or higher-income beneficiaries should be measured using the same yardsticks; however, outcomes-based payments should be adjusted to account for the impact of socioeconomic determinants. One such adjustment is to reflect performance relative to similar peer groups. Similarly, an equitable metric for cognitive or functional improvement should not be automatically discounted because individuals who can benefit from the improvement have other comorbidities that will persist despite the treatment.

The significant socioeconomic, racial, ethnic, and gender disparities at play in AD patients cannot be reflected in a single metric based on expected life years and QOL for only the patient. By not capturing the disparate experiences of patients and caregivers and recognizing how the current support system relies on low-wage and no-wage labor, the traditional approach ignores the systemic disparities affecting racial, ethnic, and economic subgroups and fails to capture the full value.

These realities necessitate the use of a value assessment approach that is flexible enough to reflect community impacts.

CAPTURE THE HEALTH-RELATED VALUE OF ALZHEIMER'S DISEASE TREATMENTS NOT ONLY FOR PATIENTS BUT ALSO FOR THEIR INFORMAL CAREGIVERS

An appropriate value assessment framework for any disease state should mirror issues of importance to those impacted by that disease. In the case of AD, traditional frameworks to assess utility use a small number of decremental stages in patients' cognitive status.³⁰ For example, many studies focus solely on decline in clinical function, assessing a patient's progression from mild to moderate to severe AD and occasionally adding in a high-level binary variable (independent vs. dependent) to signify the patient's need for full-time support.^{30,31} While this approach may correspond to clinical trial metrics, it does not align with the most significant issues for patients with AD and their caregivers. In a recent qualitative study of AD patients and their caregivers, researchers revealed that the day-to-day impacts of AD are multifaceted. While memory and forgetfulness were named the most bothersome or challenging issues for patients and their care partners during early-stage disease (e.g., mild cognitive impairment and mild AD),

issues related to activities of daily living, safety, changes in behavior or personality, and caregiver dependence rose to the forefront by later stages.³² Dementia caregivers are significantly more likely than non-dementia caregivers to report their loved one requires care not only for cognitive issues but also for long-term physical conditions, emotional or mental health problems, and behavioral issues. Caregivers are also more likely to provide assistance with all activities of daily living (ADLs), including intimate ADLs, such as incontinence issues, bathing, and feeding.³³ Value assessments in the AD space should capture the effects of treatment on these additional elements of living—even if the treatments do not affect the stages of AD.

Patients with AD require significant caregiver support, much of which is informal. These informal caregivers are often family members and loved ones of the patients, who in turn endure additional health burdens because of AD.³⁴ Family caregivers of patients have been called “the invisible second patients” of dementia due to the immense emotional, physical, and financial load they carry. AD caregiving is difficult, as the disease itself is unrelenting and the progression is often drawn out.¹⁰ According to the Family Caregiver Alliance, about 1 in 10 caregivers report declines in their own physical health due to caregiving. Caregivers report chronic conditions like heart disease, cancer, and diabetes at nearly twice the rate of non-caregivers, and between 40% to 70% of caregivers have symptoms of clinical depression.³⁵ Studies consistently show considerably worse health outcomes for family caregivers who tend to relatives with high care needs, such as those living with AD.³⁶

In traditional value assessment calculations, there is minimal consideration of these caregiver health costs and benefits. This omission from the traditional approach is a major weakness when it comes to AD. An appropriate health value framework for AD should be able to capture health-related value to whomever, patient or caregiver or community, that value accrues.

APPROPRIATELY ACCOUNT FOR CHANGES IN NON-HEALTH OUTCOMES AND ISSUES OF COMMUNITY VALUE RELATED TO AD PATIENTS AND THEIR CAREGIVERS

AD is characterized by an array of hidden costs, which necessitates a more holistic and ecological approach to measuring value for this disease state. Caregivers incur significant indirect costs. Seventy-five percent of caregiving provided for patients with AD is informal.¹⁰ In 2019, about 16.3 million informal caregivers in the US provided an estimated 18.6 billion hours of unpaid care and support to patients with AD.¹⁰

This reliance on informal or unpaid caregiving for AD generates underrecognized spillover costs. Unpaid contributions of caregivers have been valued at approximately \$244 billion¹⁰ in 2019, and recent research found that nearly one in three workers said they quit their jobs for caregiving responsibilities at some point.³⁷ Total wage losses due to leaving the labor force have been estimated at \$89,107 per affected individual for men and \$142,693 for women; when lost Social Security benefits are included, losses climb to \$233,716 for men and \$274,044 for women.³⁸ These economic burdens are magnified for certain demographics, especially women, racial and ethnic minorities, and socioeconomically depressed populations.⁹ Not only are women disproportionately affected by AD, but they also comprise two-thirds of AD caregivers.⁹ In fact, 19% of women end up leaving the workforce due to the burden of AD caregiving.³⁹ In

aggregate, indirect costs associated with this lost work and productivity are estimated to reach \$2.1 trillion between 2012 and 2040.⁴⁰

There are also costs to caregivers who remain in the workforce. Productivity losses due to caregiving burden, which is distinct from the value of unpaid caregivers, have been estimated to be between \$17 billion and \$33 billion annually, reflecting costs of absenteeism, shifts from full- to part-time work, and workday adjustments.⁴¹ This fact suggests there may be additional opportunity costs associated with caregiving that have been missed by estimates of the total costs of AD. Most family caregivers (60%) are juggling paid work and caregiving, and trends suggest that an increasing portion of family caregivers will be working age and in the labor force due to expected prevalence of AD among the aging baby boomer generation.³⁷ Caregivers are also often responsible for covering substantial out-of-pocket costs on behalf of AD patients. A 2008 report found that the average family caregiver spent \$5,531 annually on out-of-pocket caregiving expenses, which, at the time, constituted more than 10% of the median income for a family caregiver.³⁶ Another study estimated that, assuming no changes in public or private financial options for long-term support care, more than half of all long-term support spending will be covered out of pocket by individuals and their families by 2030.³⁷ This trend is especially relevant in the context of AD since as many as three quarters of all patients with dementia ultimately require care in a long-term care facility.²¹

As in other areas, disparities exist and disproportionately impact communities of color. Black and Latino communities experience AD at higher rates. These groups are expected to comprise nearly 40% of people living with AD in the US by 2030⁴² despite being projected to make up only 35% of the general population.⁴³ In 2012 alone, direct and indirect costs of AD for African Americans were estimated to total over \$71 billion, while unpaid caregiving provided by African Americans accounted for more than \$43 billion—or approximately 60% of the total cost.⁴⁴ Similarly, for Latinos, total direct and indirect costs are projected to escalate from around \$11 billion in 2012 to nearly \$30 billion in 2030 and \$105 billion by the end of 2060.⁴⁵ Working caregivers are more likely to reside in lower-income households than higher-income households, and caregivers in general are nearly twice as likely to report financial shortfalls for healthcare or medicine than non-caregivers.⁴⁶ The risk factors associated with AD suggest complex interactions with social determinants of health, some of which may not be well understood or quantified today. These realities suggest that the effects of AD on families in these communities are likely to reinforce existing disparities and generational poverty. Thus, value assessments should capture the potential for new therapies to promote health equity and help alleviate some of this societal burden.

The caregiver costs, spillover costs, and the cost of established disparities in AD stand in contrast to the small, incremental, direct Medicare costs of AD, which are estimated to be only about 11% greater relative to Medicare costs for individuals without AD.²⁰ The relative importance of these “indirect” costs in juxtaposition to the small incremental medical costs supports the view that an ecological approach may be appropriate when assessing value in AD.

The Traditional Value Assessment Framework

Currently, the most widespread approach to assessing health treatment value centers around quantifying the relationship between patient quality-of-life measures and cost of treatment. This is a form of cost-effectiveness analysis (CEA). CEAs focus on figuring out how much it costs to get a certain amount of output from a treatment (i.e., how much is the treatment worth).⁴⁷ While CEAs can be useful to compare the costs and impacts of treatment alternatives that serve the same purpose, they can fall short beyond this limited use.⁴⁷

The Institute for Clinical and Economic Review (ICER) is well-known for its reports that quantify the value of new medical treatments in the US. Its assessments stand as primary examples of the traditional CEA approach. ICER is an independent non-profit organization whose funding includes grants from government and non-profit foundations, health plans, provider groups, and private insurers.⁴⁸ ICER performs clinical and economic reviews of new treatments and medical technologies and makes recommendations to payers regarding price and benefit coverage. ICER explicitly utilizes a cost-utility approach (a form of CEA) in its assessments.

ICER has gained influence and respect among both public and private sector healthcare payers over the past five years. In 2017, the Department of Veterans Affairs Pharmacy Benefits Management Services office partnered with ICER in its drug coverage and pricing negotiations with the pharmaceutical industry and to incorporate ICER findings in the Department's formulary management process.⁴⁹ The following year, CVS Health announced it would allow its Caremark clients to exclude from their formularies certain drugs that do not meet benchmark cost per quality-adjusted life year (QALY) thresholds according to ICER analyses.⁵⁰ These types of partnerships are expected to increase in the future.⁵¹

A primary mechanism used in the traditional approach to CEA is the quality-adjusted life year (QALY).⁵² The QALY is a well-known measure used to knit length of life and QOL (measured in terms of utility) into a single index. The QALY is meant to adjust the value of each year of life by health burden.

Advocates of traditional approach point out that QALYs enable direct comparison of disparate interventions and outcomes. For example, one year of perfect health is equal to 1 QALY (1 Year of Life x 1 Utility = 1 QALY), while a half year of life bedridden (assuming bedridden QOL equals 0.5) is equal to 0.25 QALY (0.5 year of life x 0.5 utility).⁵³ This means that under the QALY methodology, ten years lived bedridden are equivalent to five years lived in perfect health.⁵⁴ ICER and others use QALYs to determine the incremental utility afforded by a prospective treatment. ICER then marries this measure to a range of cost-per-QALY thresholds (\$50,000 per QALY - \$200,000 per QALY) to suggest a cost-effective price range for the treatment. A treatment whose price per QALY is higher than this predetermined range may be deemed cost ineffective and recommended for exclusion from benefits coverage.

A goal of the traditional cost-effectiveness approach is to determine if the value of an intervention justifies its cost. To do this, CEA compares one intervention to another (perhaps to the standard of care) by assessing how much it costs to achieve an incremental gain in health, usually measured as improved QOL or additional years of life. The QALY is the long-standing

outcome measure of choice for this calculus.⁵⁵ The QALY is a single metric and relies primarily on point-in-time system means to assess economic value. ICER notes that this approach struggles to represent “the diversity of patient outcomes and values.”⁵² As it points out, “there will always be an inherent tension between average findings in clinical studies and the uniqueness of every patient,”⁵² and that this “value framework does not solve these tensions, but neither does it obscure them.”⁵²

Shortcomings of the Traditional Framework

QALYS AND THE CHALLENGES OF UTILITY MEASUREMENT IN ALZHEIMER’S DISEASE

QALYs for particular conditions are based on surveys of people with and without the condition of interest who are asked to evaluate trade-offs among health conditions assuming a “fair trade.” The results are called health state preference values. For example, if a group of people decided that a full year in perfect health had the same value as two years in a wheelchair, the “utility” of being in a wheelchair would be 0.5. In this illustration, a person expected to live in perfect health for 5 years would be assigned 5 QALYs, while someone expected to live in a wheelchair for 4 years would be assigned 2 QALYs. If a \$100,000 treatment gave the wheelchair-confined person perfect health for 5 years, the cost per QALY gained would be $\$100,000/(5-2)$ or \$33,333.

Measuring utility is difficult. Not only do people often misunderstand utility scales, but dissimilar populations may also evaluate conditions differently.²⁷ For example, a violinist may view deafness as much worse than being wheelchair bound, but a golfer may have the opposite view. Furthermore, a patient’s outlook on utility set before a condition is diagnosed or progresses is likely to be different from their view of utility once they have acclimated to the condition. As ICER notes, “There will always be diversity in the way that patients view the balance of risks and benefits of different treatment options.”⁵²

One tool relied upon extensively to evaluate utility for QALY calculations is the EQ-5D questionnaire, which assesses 5 domains of QOL – mobility, self-care, usual activities, pain/discomfort, and anxiety/depression – using multiple levels (three to five depending on the version) to measure patients’ perception of their difficulty or severity within the domain (i.e., no pain/moderate pain/extreme pain).⁵⁶ Yet, the EQ-5D’s simplicity belies the inherent nuance of patients’ situations. Patients with chronic conditions may respond with uniformly low scores in a domain, but this result may not be directly related to the patient’s experience of the disability itself. Assessments may also be impacted by external factors. For example, a patient’s negative experience of reduced mobility could be driven primarily by a lack of accessibility in his or her environment rather than by the reduced mobility itself.⁵⁷ A comparable patient in a more favorable environment could respond to the questionnaire differently. Similarly, other contextual factors, such as initial health status or financial insecurity, are neither captured by nor accounted for by the EQ-5D.

Utility measurement is particularly tricky in conditions like AD in which there are fundamental challenges to discerning elements of value to patients and their caregivers. The degenerative

nature of AD often results in caregivers being asked to assess QOL for patients. However, caregivers as proxies report lower utility scores compared to those produced when patients complete the surveys themselves.⁵⁸ Most importantly, the EQ-5D has been found to be inadequate for assessing the QOL of AD patients.^{59,60} Efforts are underway by the EQ-5D developers to validate an EQ-5D supplement (EQ-HWB) that will address important aspects of AD.⁶¹

METHODOLOGIC BIASES OF QALYS AND THE TRADITIONAL APPROACH

The QALY has been critiqued by those who believe its basic methodology causes it to produce ageist, ableist or otherwise unfair results. Indeed, cost-per-QALY ratios methodologically favor younger, healthier populations that have more potential QALYs to gain.⁶² Since fewer life-years are expected to be achieved from any treatment used to assist older patients, treatments targeted toward older patients will be assessed a lower value. Similarly, since the QALY calculation discounts life years by using lower relative utilities to reflect health burden, treatments targeted at extending the lives of patients with disabilities will be worth less. The US' National Council on Disability, an independent federal agency, has long opposed the use of QALYs for this reason, saying QALY operates on a faulty premise "that life with a disability is inherently worse than life without a disability."⁵⁷

Critics have also emphasized that the QALY methodology could lead to an intrinsic preference for life-saving over life-enhancing treatments because preventive or basic long-term care interventions, such as vaccinations, generally score lower on QALY calculations than more dramatic treatments, such as hip replacements.²⁷ These issues are of particular concern in the AD realm as patients are overwhelmingly of advanced age and generally experience many years of reduced function after initial diagnosis. In addition, some AD treatments being developed are geared toward symptomatic improvement rather than cognitive enhancement or lifespan extension.⁶³ As described above, symptomatic improvement may also have a great value to caregivers, which the QALY approach does not consider.

ICER recently introduced the evLYG (Equal Value of Life Years Gained) to address concerns that the lower QALY starting point of people with disabilities can distort results. evLYGs simply remove utility weighting from the QALY calculation, such that any year gained from a treatment is counted in full regardless of health burden. evLYGs are a traditional "life insurance"-style metric that dates from the 19th century. For instance, an intervention that hypothetically adds two years to the life of a patient with cancer will receive the same evLYGs as an intervention that adds two years life to a patient without cancer – 2 evLYGs.⁵² evLYGs do not avoid favoring conditions or groups with greater expected future lifespan or those whose lifespan is not reduced by an existing condition; still, according to ICER, this metric will be reviewed alongside the QALY and will remove the possibility that interventions that add more time at lowered function will be deemed less valuable.⁵² It remains to be seen how materially this measure will influence ICER's final assessments. Research has shown that use of unadjusted life years as opposed to quality-adjusted life years produces substantially similar cost-effectiveness estimates.⁶⁴

The standard utility value for QOL ranges from 0 to 1, where 1 is perfect health and 0 is death; the latter brings the QOL of death into synchrony with future life years, which is 0 for someone who has died. Some researchers believe the QOL scale should include negative values to reflect QOL worse than death.^{65,66} The use of QOL less than 0 increases the potential gain from certain therapies, as moving from a negative number to a positive number is more than moving from 0 to the same positive number. This shift could increase the value of some interventions and may better reflect patients' or caregivers' expectations of the patient's experience of certain conditions.

The QALY-based approach is increasingly used by payers and health systems to make benefit coverage/reimbursement and supply decisions.⁶⁷ Consistent with these uses, it does not account for the societal value of treatments or the effect of the treatment on any other stakeholders because it only considers survival and QOL as the measure of benefit or effectiveness. Over the years, ICER has attempted to expand beyond the payer and health system use cases, most recently by adding a societal base case assessment and introducing a mechanism by which other benefits or contextual considerations can be reviewed and used to inform cost-per-QALY thresholds used in the value assessment. ICER calls these "Potential Other Benefits or Disadvantages and Contextual Considerations".⁵² Theoretically, this "societal co-base case" will be driven by the QALY and medical costs but will also include additional elements related to caregiving, lost earnings, productivity, social services, necessary home improvements, and more.⁵ The "Potential Other Benefits or Disadvantages and Contextual Considerations" will enable ICER to consider whether certain variables, such as a treatment's unique balance of risks and benefits or a new mechanism of action, should be credited to the cost-effectiveness price range for an assessed treatment.

It is unclear how these new mechanisms will work in practice. ICER has noted that the societal co-base case will need to demonstrate at least a 20% change in the incremental cost-effectiveness ratio from the base case analysis to be considered in its discussion. How this incremental change will be calculated and the rationale for the 20% threshold are not clear. Meanwhile, the value of any one potential other benefit, disadvantage, or contextual consideration is unquantified in ICER's assessment framework.⁵² Ultimately, ICER's mechanism is still reliant on the QALY and is weighted heavily on direct healthcare costs, and its methodology is incomplete for conditions that cannot be evaluated fairly or comprehensively by these two elements alone.

TRADITIONAL QALY-BASED APPROACHES CAN REINFORCE DISPARITIES

Traditional cost-effectiveness approaches rely on QALYs, but their use puts payers and healthcare decisionmakers at risk of further codifying racial, ethnic, and socioeconomic inequalities. Minority, low-income, and rural populations often experience comparatively poorer health outcomes and lower life expectancies compared to US population averages. As noted earlier, even within AD, Black/African American and Hispanic/Latino communities are disproportionately affected, with the disease striking at younger ages and more often than among whites. Consequently, treatments are likely to elicit different (and lower) incremental values for these patients.

Historically, QALYs differ for disadvantaged populations. For example, one study found that along with higher per capita health expenditures, greater inpatient costs, and greater ER visits, Black patients with both type 2 diabetes (T2D) and visual Impairment had 3.5 fewer future QALYs than white patients with these ailments. This difference was found to be driven by racial differences in life expectancy.⁶⁸ Another recent study found that although Black Americans possess higher rates of severe osteoarthritis (OA), OA pain, and related risk factors, Black men gained 7.8 fewer QALYs from procedures to treat OA than white men, while Black women gained 7.5 fewer QALYs than white women.⁶⁹

QALYs rely on population means to assess utility and value, which results in treatments being overvalued for some subsets of patients and overvalued for others. When a condition is more prevalent in a group subject to negative disparities, the historical status quo of QOL and life expectancy can generate low estimates of value. Systemic disparities in health outcomes can result in entire populations falling to one end of the data distribution or the other, resulting in an inaccurate assessment of value being imposed on an entire swath of the population. Therefore, any decision regarding resource rationing based on this assessment is likely to reinforce the structural biases associated with the disparities. While QALYs have been heralded as an egalitarian measure (“A QALY is a QALY is a QALY”)⁵⁴, unintended methodological bias often reinforces disparities. This disparities concern has been raised by patient advocates and researchers alike, and more work is needed to remedy it.^{70–72} In responses to comments on their sickle cell disease treatment evidence report, ICER acknowledged this quantitative shortcoming in its framework, pointing out that it attempts to address these concerns using qualitative means. ICER’s approach consists of articulating the existence of systemic disparities in their final write up and recommending to their audience that “decision-makers may give additional weight to treatments with the potential to ameliorate such disparities.”⁷²

QALYs also have arithmetic implications that may not reflect patients’ or society’s preferences. If applied to individuals, QALYs lead to the conclusion that the same therapeutic improvement is worth less when applied to someone with an unrelated disability than when applied to a like person without the disability. This is because the person with the disability starts with a lower value for QOL, so their QOL after adding an improvement will also be lower. Also, arithmetically, improving one person’s QALY by a certain amount can look the same as half of that improvement applied to 2 people, but the public or individuals may not consider the two outcomes to be equivalent. This has important implications for payer analyses that look at a therapeutic’s assessed value over a population, in that a drug that creates a marginal improvement in a large population may be assessed as more valuable than a treatment with a large improvement for a narrow population. The conclusion of such arithmetic operations may not correspond to societal preferences when the choices are viewed holistically, or to the collection of individual preferences, which is a finding from the study of behavioral economics.⁷³ This construct has long been a concern for treatments for rare diseases.⁵⁷

Researchers have reported that literature measuring utility in AD tends to rely too heavily on cognition as opposed to other qualities to describe disease progression.³⁰ This means that utilities derived from these studies may produce results that are disconnected from the real

drivers of patients' (and their caregivers') health burden, such as deteriorations in continence, mobility, and neuropsychiatric status.^{32,74} A stage-shift model based largely on cognitive decline to assess the value of treatments in AD⁷⁵ can under-value the importance of treatments that improve QOL but do not slow or reverse cognitive impairment.

Similarly, traditional cost-effectiveness frameworks struggle to appropriately account for the value of diagnostics or early diagnosis. Mild cognitive impairment may be a precursor to AD in some cases, and studies have already begun to demonstrate the potential financial value of early patient identification and care planning.¹⁸ Value assessments of emerging diagnostic tests are often more challenging to conduct than assessments of therapeutics, due to relatively sparse information about the relationship between diagnosis and long-term care outcomes.⁷⁶ This is especially true for conditions like AD for which there are few interventions available to delay disease progression even when identified early.¹⁷ Advocates point to the value of diagnostics to physicians in terms of clinical research, care planning, and defensive medicine.⁷⁷

The lack of recent QOL literature for certain conditions is another challenge. For example, ICER's source for the utilities it plans to use in its next AD-related assessment is over 20 years old.⁷⁵ The work of choosing from among published QOL metrics, deciding when data is too old, and deciding to update existing survey data are all challenges of utilizing the traditional value assessment approach.

CAREGIVER CONSIDERATIONS ARE CRITICAL FOR ALZHEIMER'S DISEASE

Informal caregiving is the de facto standard of care for most AD patients – 92% of older adults with dementia receive help from family members or other informal care providers.⁹ Importantly, caregivers' health and wellness is linked to the health status of their disabled relatives. Research has demonstrated an association between lower caregiver QOL and increasing patient dependency,⁷⁸ and caregiver mortality risk has been seen to increase with the hospitalization of a dependent spouse.³⁵ These physical and emotional impacts were estimated to result in nearly \$9.7 billion in healthcare costs in 2014 alone.⁷⁹ The majority of the reported nearly \$550 billion per year cost of AD is borne by patients and their families.³ As such, In conditions like AD, where the lion's share of the disease's burden falls on caregivers rather than on healthcare payers, the societal impact is difficult to ignore when assessing value of treatment.

Attempts have been made to expand the traditional approach to value assessment to include some elements of AD's societal impact. For example, ICER has stated that it will include caregiver and family productivity outcomes in its societal "co-base case" analysis when empirical data are available.⁵² However, ICER has noted that caregiver and family utilities are difficult to incorporate into traditional QALY-based modeling "because there is no established way to determine how to aggregate QALYs across multiple family members in a way that is consistent and can be applied to opportunity cost thresholds."⁵² Furthermore, ICER cautions that incorporation of caregiver utilities into models can produce counterintuitive findings, such as results that suggest caregivers would be better off were their charges to die quickly. They point out that these are "in total opposition to caregivers' deepest beliefs and hopes for extended time with a family member."⁵² These responses suggest that the traditional approach to value

assessment cannot easily account for caregiver and family factors, even when deliberately augmented to accommodate the societal perspective.

DIRECT HEALTHCARE COSTS ARE A SMALL PORTION OF THE ECONOMIC IMPACT OF ALZHEIMER'S DISEASE

The traditional approach does not consider the financial implications inherent to the complicated relationship between Medicare and Medicaid for many older adults with AD. A lack of coordination between Medicare and Medicaid can often create conflicting incentives for long-term care providers, leading to duplicate services, gaps in coverage, and inconsistent delivery of services or quality of care for dual-eligible individuals across states.⁸⁰ As a federal program, Medicare provides insurance benefits for qualifying individuals aged sixty-five or older regardless of income status and also covers younger people starting 24 months after they qualify for Social Security Disability Insurance (SSDI). Medicaid is a state-based program funded in part by the federal government and offers acute care and long-term care coverage to low-income populations. However, Medicare covers few long-term care services, so Medicaid covers the bulk of long-term care costs for Medicare beneficiaries who also qualify for Medicaid (dual eligible).⁸⁰ The complicated relationship between Medicare and Medicaid means that future AD therapies that reduce long-term care needs could reduce Medicaid spending while increasing medical spend for Medicare .

While eligibility varies from state to state, there are specific income (or asset) requirements for individuals to qualify for Medicaid. In some states, if individuals do not meet the financial requirement, they can elect to “spend-down” income and assets.⁸¹ People who spend-down to Medicaid eligibility are disproportionately lower income and have substantially fewer assets than people who do not spend down. In a study of data merged from the Health and Retirement Study and Medicare from 1996-2008, almost 10% of Medicaid beneficiaries age 50 and up in their sample needed to spend down to meet Medicaid eligibility requirements. Over half of these individuals used some form of long-term care service including personal care services or nursing facilities.⁸²

The financial impact of this spend down on the intergenerational transfer of wealth especially among low-income populations is a controversial topic. Some research suggests that the spend down itself does not typically move individuals from moderate to low wealth and that low income prior to retirement is a larger contributor to a decline in wealth after age 65, but other research indicates that the transfer of assets to family members from lower middle-class individuals may be obscuring results.^{82,83} In states with spend-down provisions, the prevalence of co-residence among adult children and older family members decreases by 1 to 4 percentage points, with a corresponding increase in nursing home care.⁸⁴ Patients with AD and their families spent an average of \$10,495 annually out-of-pocket for AD care, with those residing in long-term care facilities or assisted living facilities spending 6 times as much as community-dwelling patients with AD and related dementias.²¹ Mean out-of-pocket costs for the last five years of life totaled \$61,522 for individuals with dementia with nearly 32% of their expenditures out-of-pocket.²¹

Clearly, the economic impact of AD extends far beyond the direct medical costs that are the focus of the traditional approach to value.

Relevant Techniques to Measure Societal Value for Alzheimer's Disease

The enhanced value assessment framework described in this paper is an ecological/societal perspective that also separates the question of the value of a treatment from who pays for it and who receives payment. If a societal value were determined for a new treatment, policymakers and payers could collaborate on how to best balance who receives payments and who pays costs. This paper does not address the distribution of revenue and cost. However, there are concerns that the traditional CEA approach means that treatments with high societal value, but lower healthcare payer value could be disadvantaged through usage restrictions, patient cost-sharing, or other means.

Analogues of broad funding societal value include social funding of medical education, public health, charity care, innovative medical research, and the stability of organizations. For example, the New York Health Care Reform Act (HCRA) of 1996 implemented a tax on insurers' payments to providers to fund healthcare for the uninsured and indigent as well as health policy initiatives, such as expanded and improved delivery of primary care health services and promotion of healthcare in rural areas.⁸⁵ Similarly, states charge insurers fees to fund insolvency pools to ensure there are funds available in the event that an insurance company goes bankrupt.⁸⁶ States fund pharmaceutical assistance programs to help support residents who lack insurance coverage or are without the financial ability to pay for cost sharing.⁸⁷ Clearly, there is willingness to creatively distribute costs and creatively capture revenue among many stakeholders when an issue is deemed of high value to society.

The challenge of measurement affects any value system. One approach is to use comprehensive cost-benefit assessment, which could allow for the capture of all components of societal value. In contrast to CEA techniques, cost-benefit analyses (CBAs) ask whether the benefits outweigh the costs of a given treatment. Numerous CBA methodologies have been proposed that take a more holistic approach to demonstrating value for money in healthcare. For instance, social return on investment (SROI) is a CBA methodology that captures both the health and non-health impacts of a treatment using a "triple bottom line" approach that estimates the social, economic, and environmental value of an intervention.⁴⁷ In other words, an SROI methodology offers a way of placing value on personal, social, and community outcomes, not just economic ones.⁸⁸ Similarly, multiple-criteria decision analysis (MCDA) or deliberative appraisal approaches allow multiple perspectives to converse simultaneously, such that the overarching impact of an intervention can be assessed. Ultimately, the key feature these methodologies have in common is that they leave space for community health and societal value in the assessment of a treatment's value.

Quantitative metrics have been proposed for social value for use in economic healthcare analyses. One, the Relative Social Willingness to Pay (RS-WTP) instrument, measures individuals' willingness to pay for a service relative to another service from a social perspective.⁸⁹ Essentially the RS-WTP tool asks respondents to divide a hypothetical

government budget between two services, where the two services have different end points (e.g., “How would you allocate \$50,000 between Service A and Service B such that the amounts given for each service represent the value of the benefits to health from Service A vs Service B?”). Respondents are actively asked to take everything they believe to be important into account, including non-health factors, when allocating this hypothetical budget. This tool generates both a ratio of relative social value and an index value, which makes it an appealing option to explore for economic evaluations. Furthermore, it does not inherently favor lifesaving over life-improving interventions and leaves room for other elements of value to permeate the value assessment calculation.

Analogs can also be used to demonstrate the societal value of various interventions. For example, there is a growing effort to shuttle resources toward the mitigation of disparities, as these inequalities have been established as costly to the whole of society. If one were looking to understand society’s willingness to pay for the repair of dysfunctional ecologies, one could look at responses to, and resource expenditures for, other issues that the US has already attempted to fix, such as the Superfund for pollution or funding for the COVID public health emergency. Likewise, the US dedicates public and private resources to the care of people who are severely mentally disabled. These costs could be used as benchmarks to compare to other interventions for the long-term care and support of individuals with special care needs like AD. While these analogs may have been developed using political means and perhaps not based on a consistent framework, they can help clarify how society values complex challenges practically and with numerous influences at play.

The movement toward fully integrated care for people with long-term care needs, such as AD, includes pilots with new types of payer organizations that are responsible for both medical and long-term care services. The definition of payer liabilities for such organizations expands beyond direct healthcare costs to include supportive services, which means these organizations’ financial interests are more aligned with the holistic perspective than a traditional payer’s are. If these programs expand beyond the pilot phase, there will be a need to reformulate the “payer perspective” beyond the traditional approach for participating organizations. For example, Medicare does not cover long-term care services, which are covered by Medicaid only for eligible persons, but pilot programs are now using a Medicare Advantage plan known as a Medicare-Medicaid Plan to seamlessly provide patients with all necessary Medicare and Medicaid services. Similarly, Medicare Special Needs Plans, known as SNPs, can provide both Medicare and Medicaid services through separate contracts with Medicare and a state’s Medicaid agency.⁹⁰ Clearly, different payers can have vastly different, intersecting and overlapping scopes of financial responsibility, especially for patients with AD. If this movement toward integrated care becomes more widespread, the societal approach may be useful as a standard way to assess value across diverse payers.

Additional Approaches to Evaluating Therapeutic Value in Alzheimer's Disease

Other countries use traditional methods to provide independent health technology assessments (HTAs), including the cost-effectiveness evaluations of new treatments. The National Institute for Health and Clinical Excellence (NICE) releases evidence-based recommendations to the United Kingdom's National Health Service (NHS) for various disease-states. These recommendations are authored by independent committees comprised of various healthcare stakeholders in England and Wales.⁹¹ NICE (1999) predates ICER (2006) by seven years, and it has been suggested that ICER may have adopted NICE's structure for clinical and economic reviews with an emphasis on cost-per-QALY.⁹² ICER has also referenced NICE guidelines in their assessments, including their 2012 assessment on dementia, *Diagnostic Tests for Alzheimer's Disease: Generating and Evaluating Evidence to Inform Insurance Coverage Policy*, in which ICER did not recommend AD diagnostic testing because it found limited research to indicate that "the effects of early diagnosis in AD and similar conditions on anxiety/stress, financial planning, relationships, etc. are relatively short-lived."⁹³ Despite the significant differences between the US and UK healthcare systems, NICE and ICER use very similar approaches, and the limitations of the traditional, QALY-based approach to value assessment apply to both.

Germany's approach to balancing cost-effectiveness with the needs and concerns of caregivers and patients does not use QALYs. The German healthcare system is comprised of both statutory health insurance (SHI), covering 90% of the population, as well as private insurance plans, which cover the remaining 10%. The benefits covered by SHI are determined by the Federal Joint Committee (G-BA).⁹⁴ Despite using many of the same traditional cost-effectiveness approaches as ICER and NICE, the G-BA captures broader public health system interests in its analyses. Germany has a diverse landscape of AD and dementia advocacy groups, including organizations of people with early-stage dementia, which are actively included in parliamentary committee hearings and governmental deliberations on topics of drug coverage and costs.⁹⁵ The integration of these groups' input with cost-effectiveness analyses provides a valuable perspective for the decisionmakers that would be lost using traditional QALY-based metrics alone.⁹⁵

The US Patient-Centered Outcomes Research Institute (PCORI), an independent nonprofit, nongovernmental organization in Washington, DC, was authorized by Congress in 2010 to "improve the quality and relevance of evidence available to help patients, caregivers, clinicians, employers, insurers, and policy makers make better-informed health decisions."⁹⁶ PCORI is a prominent public funder of comparative clinical effectiveness research, which is research comparing the benefits and harms of alternative treatments or care delivery. PCORI was reauthorized by the Further Consolidated Appropriations Act of 2020, which expanded its authority to fund research that considers economic impacts.⁹⁷ In response to this expansion, PCORI released a set of four "Principles for the Consideration of the Full Range of Outcomes Data in PCORI-Funded Research" in 2021 to guide grant applicants. PCORI's principles are [Italics in original]⁹⁷:

1. Considering the full range of outcomes *important to patients and caregivers*, including potential burdens and economic impacts, is central to PCORI-funded research.
2. PCORI-funded research may consider the full range of outcomes *relevant to other stakeholders*, when these outcomes have a near-term or longer-term impact on patients.
3. The collection of data on potential burdens and economic impacts of intervention options must be *appropriate and relevant to the clinical aims of the study*.
4. PCORI may support the conduct of certain types of economic analyses, as part of a funded research study or independently, to enhance the relevance and value to patients and other stakeholders of information PCORI-funded investigators collect on potential burdens and economic impacts burdens.

We note that PCORI's authorizing law prohibits it from funding research that makes coverage or payment recommendations or uses QALY-based financial thresholds. While PCORI does not have authority to set policy, PCORI is credited with influencing both FDA's and CMS' approaches to engaging with patients.⁹⁸

Another approach that is attracting interest is value-based or outcomes-based contracting, where payment is contingent upon the success of the therapy.^{99,100} We note that we have not addressed payment issues in this paper, and outcomes-based contracts have not been implemented broadly for individual therapies.

Conclusions

The traditional, QALY-based approaches to value in healthcare are not well-suited to capture the value of treatment for conditions, such as AD, which bring complex societal and community burdens linked to disparities. This paper describes an alternative, ecologic approach.

The ecologic approach to assessing health will undoubtedly evolve, and the development of relevant quantification methods is certainly consistent with our principles. Some salient issues for future research include the health and social value to communities and families derived from parents and grandparents who may be relieved of care duties and the value to society of relieving racial and ethnic disparities.

The issues that we have raised in this paper apply beyond AD and related dementias to other conditions like Parkinson's disease, traumatic brain injury, and amyotrophic lateral sclerosis. Based on the information in this report, the authors recommend prioritizing the development of alternative, holistic approaches to value rather than persisting with band-aids to the current methods.

Limitations and Notes

Bruce Pyenson, Pamela Pelizzari, and Rebecca Smith are employees of Milliman, Inc., and Helen Latimer was an employee at the time this work was performed. This report is the work of

the authors, who do not endorse any legislation or product. It does not represent the opinions of Milliman. The authors have no financial interests or stakes in measurement systems based on these concepts.

Guidelines issued by the American Academy of Actuaries require members to identify their qualifications for professional work. Bruce Pyenson is a member of the American Academy of Actuaries and meets the qualification standards to issue this report.

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References

1. Wimo A, Ballard C, Brayne C, et al. Health economic evaluation of treatments for Alzheimer's disease: Impact of new diagnostic criteria. *J Intern Med*. 2014;275(3):304-316. doi:10.1111/joim.12167
2. Vernon J, Ph D. Alzheimer ' s Disease and Cost-effectiveness Analyses : Ensuring Good Value for Money ?
3. Gustavsson A, Pemberton-Ross P, Gomez Montero M, Hashim M, Thompson R. Challenges in demonstrating the value of disease-modifying therapies for Alzheimer's disease. *Expert Rev Pharmacoeconomics Outcomes Res*. 2020;20(6):563-570. doi:10.1080/14737167.2020.1822738
4. El-Hayek YH, Wiley RE, Khoury CP, et al. Tip of the Iceberg: Assessing the Global Socioeconomic Costs of Alzheimer's Disease and Related Dementias and Strategic Implications for Stakeholders. *J Alzheimer's Dis*. 2019;70(2):323-341. doi:10.3233/JAD-190426
5. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: Second panel on cost-effectiveness in health and medicine. *JAMA - J Am Med Assoc*. 2016;316(10):1093-1103. doi:10.1001/jama.2016.12195
6. Ken Lee KH, Matthew Austin J, Pronovost PJ. Developing a Measure of Value in Health Care. *Value Heal*. 2016;19(4):323-325. doi:10.1016/j.jval.2014.12.009
7. Towse A, Barnsley P. Approaches to identifying, measuring, and aggregating elements of value. *Int J Technol Assess Health Care*. 2013;29(4):360-364. doi:10.1017/S0266462313000524
8. National Institute on Aging (NIA), National Institutes on Health (NIH). Alzheimer's Disease Fact Sheet. Published 2019. Accessed February 26, 2021. <https://www.nia.nih.gov/health/alzheimers-disease-fact-sheet>
9. Alzheimer's Association. *2020 Alzheimer's Disease Facts and Figures*. Vol 16.; 2020. doi:10.1002/alz.12068
10. Wong W. Economic burden of Alzheimer disease and managed care considerations. *Am J Manag Care*. 2020;26(Suppl 8):S177-S183. doi:10.37765/ajmc.2020.88482
11. Scheyer O, Rahman A, Hristov H, et al. Female Sex and Alzheimer's Risk: The Menopause Connection. *J Prev Alzheimer's Dis*. 2018;5(4):225-230. doi:10.14283/jpad.2018.34
12. Lines LM, Wiener JM. *Racial and Ethnic Disparities in Alzheimer's Disease: A Literature Review*.; 2014.
13. Taylor CA, Bouldin ED, McGuire LC. Subjective Cognitive Decline Among Adults Aged ≥45 Years — United States, 2015–2016. *MMWR Morb Mortal Wkly Rep*. 2018;67(27):753-757. doi:10.15585/mmwr.mm6727a1
14. Then FS, Luck T, Villringer A, Angermeyer MC, Riedel-Heller SG. Compression of dementia morbidity by higher education. *Alzheimer's Dement*. 2015;11(7S_Part_4):P201-P201. doi:10.1016/j.jalz.2015.07.193
15. Murray CJL, Mokdad AH, Ballestros K, et al. The state of US health, 1990-2016: Burden of diseases, injuries, and risk factors among US states. *JAMA - J Am Med Assoc*.

- 2018;319(14):1444-1472. doi:10.1001/jama.2018.0158
16. Angelucci F, Spalletta G, Iulio F, et al. Alzheimers Disease (AD) and Mild Cognitive Impairment (MCI) Patients are Characterized by Increased BDNF Serum Levels. *Curr Alzheimer Res.* 2010;7(1):15-20. doi:10.2174/156720510790274473
 17. Levey A, Lah J, Goldstein F, Steenland K, Bliwise D. Mild cognitive impairment: An opportunity to identify patients at high risk for progression to Alzheimer's disease. *Clin Ther.* 2006;28(7):991-1001. doi:10.1016/j.clinthera.2006.07.006
 18. Robinson RL, Rentz DM, Andrews JS, et al. Costs of Early Stage Alzheimer's Disease in the United States: Cross-Sectional Analysis of a Prospective Cohort Study (GERAS-US). *J Alzheimer's Dis.* 2020;75(2):437-450. doi:10.3233/JAD-191212
 19. Jutkowitz E, Kane RL, Gaugler JE, MacLehose RF, Dowd B, Kuntz KM. Societal and Family Lifetime Cost of Dementia: Implications for Policy. *J Am Geriatr Soc.* 2017;65(10):2169-2175. doi:10.1111/jgs.15043
 20. Pyenson B, Sawhney TG, Steffens C, et al. The real-world medicare costs of alzheimer disease: Considerations for policy and care. *J Manag Care Spec Pharm.* 2019;25(7):800-809c. doi:10.18553/jmcp.2019.25.7.800
 21. Deb A, Thornton JD, Sambamoorthi U, Innes K. Direct and indirect cost of managing alzheimer's disease and related dementias in the United States. *Expert Rev Pharmacoeconomics Outcomes Res.* 2017;17(2):189-202. doi:10.1080/14737167.2017.1313118
 22. Afram B, Stephan A, Verbeek H, et al. Reasons for Institutionalization of People With Dementia: Informal Caregiver Reports From 8 European Countries. *J Am Med Dir Assoc.* Published online 2014. doi:10.1016/j.jamda.2013.09.012
 23. Hebert LE, Weuve J, Scherr PA, Evans DA. Alzheimer disease in the United States (2010-2050) estimated using the 2010 census. *Neurology.* 2013;80(19):1778-1783. doi:10.1212/WNL.0b013e31828726f5
 24. Lin PJ, D'Cruz B, Leech AA, et al. Family and Caregiver Spillover Effects in Cost-Utility Analyses of Alzheimer's Disease Interventions. *Pharmacoeconomics.* 2019;37(4):597-608. doi:10.1007/s40273-019-00788-3
 25. Harris J. QALYfying the value of life. *J Med Ethics.* 1987;13(3):117-123. doi:10.1136/jme.13.3.117
 26. Rawles J. Castigating QALYs. *J Med Ethics.* 1989;15(3):143-147. doi:10.1136/jme.15.3.143
 27. Pettitt DA, Raza S, Naughton B, et al. The Limitations of QALY: A Literature Review. *J Stem Cell Res Ther.* 2016;06(04). doi:10.4172/2157-7633.1000334
 28. John TM, Millum J, Wasserman D. How to Allocate Scarce Health Resources Without Discriminating Against People With Disabilities. *Econ Philos.* 2017;33(2):161-186. doi:10.1017/S0266267116000237
 29. MedPac. *Applying the Commission's Principles for Measuring Quality: Population-Based Measures and Hospital Quality Incentives.*; 2018. http://medpac.gov/docs/default-source/reports/jun18_ch7_medpacreport_sec.pdf?sfvrsn=0
 30. Shearer J, Green C, Ritchie CW, Zajicek JP. Health state values for use in the economic evaluation of treatments for alzheimers disease. *Drugs and Aging.* Published online 2012. doi:10.2165/11597380-000000000-00000

31. Green C, Handels R, Gustavsson A, et al. Assessing cost-effectiveness of early intervention in Alzheimer's disease: An open-source modeling framework. *Alzheimer's Dement.* 2019;15(10):1309-1321. doi:10.1016/j.jalz.2019.05.004
32. Dibenedetti DB, Slota C, Wronski SL, et al. Assessing what matters most to patients with or at risk for Alzheimer's and care partners: A qualitative study evaluating symptoms, impacts, and outcomes. *Alzheimer's Res Ther.* 2020;12(1):1-15. doi:10.1186/s13195-020-00659-6
33. National Alliance for Caregiving. *Dementia Caregiving in the US.*; 2017. https://www.caregiving.org/wp-content/uploads/2020/05/Dementia-Caregiving-in-the-US_February-2017.pdf
34. Brodaty H, Donkin M. Family caregivers of people with dementia. *Dialogues Clin Neurosci.* Published online 2009. doi:10.31887/dcons.2009.11.2/hbrodaty
35. Family Caregiver Alliance. Caregiver Health: A Population at Risk. Accessed March 4, 2021. <https://www.caregiver.org/resource/caregiver-health/>
36. Houser A, Gibson MJ. Valuing the invaluable: the economic value of family caregiving, 2008 update. *PPI Insight Issues.* 2008;(13):1-8. <http://proxy-remote.galib.uga.edu/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=gnh&AN=122620&site=eds-live>
37. Reinhard SC, Feinberg LF, Houser A, Choula R, Evans M. Valuing the Invaluable: 2019 Update - AARP Insight on the Issues. 2019;(November).
38. MetLife Mature Market Group, National Alliance for Caregiving, The University of Pittsburgh Institute on Aging. *The MetLife Study of Working Caregivers and Employer Health Costs: Double Jeopardy for Baby Boomers Caring for Their Parents.*; 2011. <https://www.caregiving.org/wp-content/uploads/2011/06/mmi-caregiving-costs-working-caregivers.pdf>
39. Alzheimer's Association. Women and Alzheimer's. Accessed March 18, 2021. <https://www.alz.org/alzheimers-dementia/what-is-alzheimers/women-and-alzheimer-s>
40. Super N, Ahuja R. *Reducing the Cost and Risk of Dementia.*; 2019. <https://milkeninstitute.org/reports/reducing-cost-and-risk-dementia>
41. Family Caregiver Alliance. *Caregiver Statistics: Work and Caregiving.*; 2016. <https://www.caregiver.org/resource/caregiver-statistics-work-and-caregiving/>
42. Aranda MP, Vega WA, Richardson JR, Resendez J. *Priorities for Optimizing Brain Health Interventions Across the Life Course in Socially Disadvantaged Groups.*; 2019. https://www.usagainstalzheimers.org/sites/default/files/2019-10/fiu_paper_10.18.19%281%29.pdf
43. Vespa J, Medina L, Armstrong D. *Demographic Turning Points for the United States: Population Projections for 2020 to 2060.*; 2020. <https://census.gov/programs-surveys/popproj.html>
44. Gaskin DJ, LaVeist TA, Richard P. *The Costs of Alzheimer's and Other Dementia for African Americans.*; 2013. https://www.usagainstalzheimers.org/sites/default/files/USA2_AAN_CostsReport.pdf
45. Wu S, Vega WA, Resendez J, Jin H. *Latinos & Alzheimer's Disease: New Numbers Behind the Crisis.*; 2016. https://roybal.usc.edu/wp-content/uploads/2016/10/Latinos-and-AD_USC_UsA2-Impact-Report.pdf

46. Witters D, Liu D. Poor Financial Well-Being for Working Caregivers. *Gallup*. <https://news.gallup.com/poll/238961/poor-financial-working-caregivers.aspx>. Published September 17, 2018.
47. Banke-Thomas AO, Madaj B, Charles A, Van Den Broek N. Social Return on Investment (SROI) methodology to account for value for money of public health interventions: A systematic review. *BMC Public Health*. 2015;15(1):1-14. doi:10.1186/s12889-015-1935-7
48. Institute for Clinical and Economic Review (ICER). Independent Funding. Published 2021. Accessed March 24, 2021. <https://icer.org/who-we-are/independent-funding/>
49. Institute for Clinical and Economic Review. The Institute for Clinical and Economic Review to Collaborate With the Department of Veterans Affairs' Pharmacy Benefits Management Services Office. Published online 2017. <https://icer-review.org/announcements/va-release/>
50. CVS Health. Current and Future Approaches to Making Drugs More Affordable. 2018;(August).
51. Cohen J. ICER's Growing Impact On Drug Pricing And Reimbursement. *Forbes*. Published online April 2019. <https://www.forbes.com/sites/joshuacohen/2019/04/17/icers-growing-impact-on-drug-pricing-and-reimbursement/?sh=7598f8da6b53>
52. Institute for Clinical and Economic Review. 2020-2023 Value Assessment Framework. Published online 2020:1-76. <http://www.icer-review.org/about/support/>.
53. Prieto L, Sacristán JA. Problems and solutions in calculating quality-adjusted life years (QALYs). *Health Qual Life Outcomes*. 2003;1:1-8. doi:10.1186/1477-7525-1-80
54. Weinstein MC. A QALY is a QALY is a QALY - Or is it? *J Health Econ*. 1988;7(3):289-290. doi:10.1016/0167-6296(88)90030-6
55. US Department of Veterans Affairs. Cost-Effectiveness Analysis. Accessed March 22, 2021. <https://www.herc.research.va.gov/include/page.asp?id=cost-effectiveness-analysis>
56. EuroQol Group. About EQ-5D. Published 2021. <https://euroqol.org/eq-5d-instruments/>
57. US National Council on Disability (NCD). Quality-Adjusted Life Years and the Devaluation of Life with Disability Part of the Bioethics and Disability Series National Council on Disability. Published online 2019. www.ncd.gov
58. Orgeta V, Edwards RT, Hounsborne B, Orrell M, Woods B. The use of the EQ-5D as a measure of health-related quality of life in people with dementia and their carers. *Qual Life Res*. 2015;24(2):315-324. doi:10.1007/s11136-014-0770-0
59. Reed C, Barrett A, Lebec J, et al. How useful is the EQ-5D in assessing the impact of caring for people with Alzheimer's disease? *Health Qual Life Outcomes*. 2017;15(1):1-9. doi:10.1186/s12955-017-0591-2
60. Landeiro F, Mughal S, Walsh K, et al. Health-related quality of life in people with predementia Alzheimer's disease, mild cognitive impairment or dementia measured with preference-based instruments: a systematic literature review. *Alzheimers Res Ther*. 2020;12(1):154. doi:10.1186/s13195-020-00723-1
61. EuroQol Group. EQ-HWB. EuroQol Blog. Published 2021. Accessed April 19, 2021. <https://euroqol.org/blog/eq-hwb/>
62. Neumann PJ, Cohen JT. QALYs in 2018-advantages and concerns. *JAMA - J Am Med Assoc*. 2018;319(24):2473-2474. doi:10.1001/jama.2018.6072

63. Cummings J, Lee G, Ritter A, Sabbagh M, Zhong K. Alzheimer's disease drug development pipeline: 2020. *Alzheimer's Dement Transl Res Clin Interv.* 2020;6(1). doi:10.1002/trc2.12050
64. Chapman RH, Berger M, Weinstein MC, Weeks JC, Goldie S, Neumann PJ. When does quality-adjusting life-years matter in cost-effectiveness analysis? *Health Econ.* 2004;13(5):429-436. doi:10.1002/hec.853
65. Harrison MJ, Davies LM, Bansback NJ, et al. Why Do Patients with Inflammatory Arthritis Often Score States "Worse than Death" on the EQ-5D? An Investigation of the EQ-5D Classification System. *Value Heal.* 2009;12(6):1026-1034. doi:10.1111/j.1524-4733.2009.00565.x
66. Patrick DL, Starks HE, Cain KC, Uhlmann RF, Pearlman RA. Measuring Preferences for Health States Worse than Death. *Med Decis Mak.* 1994;14(1):9-18. doi:10.1177/0272989X9401400102
67. Kaltwasser J. ICER Reports Play Significant Role in Managed Care's Decision-Making, Study Finds. *Managed Healthcare Executive.* <https://www.managedhealthcareexecutive.com/view/icer-reports-play-significant-role-managed-cares-decision-making-study-finds>. Published June 16, 2020.
68. Mccollister KE, Zheng DD, Fernandez CA, et al. Racial disparities in quality-adjusted life-years associated with diabetes and visual impairment. *Diabetes Care.* 2012;35(8):1692-1694. doi:10.2337/dc11-2433
69. Kerman HM, Smith SR, Smith KC, et al. Disparities in Total Knee Replacement: Population Losses in Quality-Adjusted Life-Years Due to Differential Offer, Acceptance, and Complication Rates for African Americans. *Arthritis Care Res (Hoboken).* 2018;70(9):1326-1334. doi:10.1002/acr.23484
70. Soares MO. Is the QALY blind, deaf and dumb to equity? NICE's considerations over equity. *Br Med Bull.* 2012;101(1):17-31. doi:10.1093/bmb/lds003
71. Saalfrank MF, Wang J, Brown LM. Racial and ethnic differences in preferences for health states and the implications for cost-utility analysis. *Expert Rev Pharmacoeconomics Outcomes Res.* 2009;9(4):365-373. doi:10.1586/erp.09.27
72. Institute for Clinical and Economic Review (ICER). *Crizanlizumab, Voxelotor, and L-Glutamine for Sickle Cell Disease Response to Public Comments on Draft Evidence Report.*; 2020.
73. Kahneman D. Determinants of Health Economic Decisions in Actual Practice: The Role of Behavioral Economics. *Value Heal.* 2006;9(2):65-67. doi:10.1111/j.1524-4733.2006.00084.x
74. Lindeza P, Rodrigues M, Costa J, Guerreiro M, Rosa MM. Impact of dementia on informal care: A systematic review of family caregivers' perceptions. *BMJ Support Palliat Care.* Published online 2020:1-12. doi:10.1136/bmjspcare-2020-002242
75. Institute for Clinical and Economic Review (ICER). *Aducanumab for Alzheimer's Disease: Effectiveness and Value, Modeling Analysis Plan.* Published online 2021.
76. Mushlin AI, Ruchlin HS, Callahan MA. Costeffectiveness of diagnostic tests. *Lancet.* 2001;358(9290):1353-1355. doi:10.1016/S0140-6736(01)06417-0
77. Laszlo G. Cost-effectiveness of diagnostic tests. *Lancet.* 2002;359(9311):1065. doi:10.1016/S0140-6736(02)08071-6

78. Serrano-Aguilar PG, Lopez-Bastida J, Yanes-Lopez V. Impact on Health-Related Quality of Life and Perceived Burden of Informal Caregivers of Individuals with Alzheimer's Disease. *Neuroepidemiology*. 2006;27(3):136-142. doi:10.1159/000095760
79. Family Caregiver Alliance. Caregiver Statistics: Health, Technology, and Caregiving Resources. Published 2016. Accessed March 16, 2021. <https://www.caregiver.org/resource/caregiver-statistics-health-technology-and-caregiving-resources/>
80. Grabowski DC. Medicare and medicaid: Conflicting incentives for long-term care. *Milbank Q*. 2007;85(4):579-610. doi:10.1111/j.1468-0009.2007.00502.x
81. Thach NT, Wiener JM. An Overview of Long-Term Services and Supports and Medicaid: Final Report. 2018;(May). <https://aspe.hhs.gov/office-disability-aging-and-long->
82. Wiener JM, Anderson WL, Khatutsky G. Medicaid Spend Down: New Estimates and Implications for Long-Term Services and Supports Financing Reform. *Washington*. 2013;(0213025). http://www.rti.org/sites/default/files/resources/rti_medicaid-spend-down_3-20-13_1.pdf%5Cpapers2://publication/uuid/AE500DC9-9509-48AC-A6A0-3FE29E51E685
83. Poterba J, Venti S, Wise DA. Longitudinal determinants of end-of-life wealth inequality. *J Public Econ*. 2018;162:78-88. doi:10.1016/j.jpubeco.2018.04.008
84. Mommaerts C. Are coresidence and nursing homes substitutes? Evidence from Medicaid spend-down provisions. *J Health Econ*. 2018;59:125-138. doi:10.1016/j.jhealeco.2018.04.003
85. NY State Department of Health. 2015 HCRA Modernization Task Force Report. Published 2017. Accessed March 22, 2021. https://www.health.ny.gov/regulations/hcra/mod_report.htm
86. O.C.G.A. 33-36-9. *Georgia Insurers Insolvency Pool.*; 2010.
87. National Conference of State Legislatures. State Pharmaceutical Assistance Programs. Published 2018. Accessed March 22, 2021. <https://www.ncsl.org/research/health/state-pharmaceutical-assistance-programs.aspx>
88. Hutchinson CL, Berndt A, Gilbert-Hunt S, George S, Ratcliffe J. Valuing the impact of health and social care programmes using social return on investment analysis: How have academics advanced the methodology? A protocol for a systematic review of peer-reviewed literature. *BMJ Open*. 2018;8(12):1-5. doi:10.1136/bmjopen-2018-022534
89. Richardson J, Iezzi A, Sinha K, Khan MA, Mckie J. An Instrument for Measuring the Social Willingness to Pay for Health State Improvement. *Health Econ*. 2014;23(7):792-805. doi:10.1002/hec.2950
90. SNP Alliance. Medicare-Medicaid Plans (MMPs). Published 2021. Accessed April 6, 2021. <https://www.snपालliance.org/what-we-do/about-mmpps-and-cmmi-demonstrations/>
91. National Institute for Health and Care Excellence (NICE). *Alzheimer's Disease - Donepezil, Galantamine, Rivastigmine and Memantine (Review): Appraisal Consultation Document.*; 2010.
92. Neumann PJ, Cohen JT. America's "NICE"? *Health Affairs Blog*. <https://www.healthaffairs.org/doi/10.1377/hblog20180306.837580/full/>. Published March 12, 2018.
93. Pearson SD, Ollendorf DA, Colby JA. Diagnostic Tests for Alzheimer's Disease:

- Generating and Evaluating Evidence to Inform Insurance Coverage Policy Table of Contents. *Inst Clin Econ Rev*. Published online 2012.
94. OECD, Wenzl M, Paris V. Pharmaceutical reimbursement and pricing in Germany. 2018;(June):1-22. <http://www.oecd.org/els/health-systems/Pharmaceutical-Reimbursement-and-Pricing-in-Germany.pdf>
 95. Schicktanz S, Rimon-Zarfaty N, Raz A, Jongsma K. Patient Representation and Advocacy for Alzheimer Disease in Germany and Israel. *J Bioeth Inq*. 2018;15(3):369-380. doi:10.1007/s11673-018-9871-8
 96. Patient-Centered Outcomes Research Institute (PCORI). About Us: Our Story. Published 2021. Accessed May 10, 2021. <https://www.pcori.org/about-us/our-story>
 97. Patient-Centered Outcomes Research Institute (PCORI). Principles for the Consideration of the Full Range of Outcomes Data in PCORI-Funded Research: Principle #4. Published 2021. Accessed May 10, 2021. <https://www.pcori.org/research-results/about-our-research/principles-consideration-full-range-outcomes-data-pcori-funded-research#content-7815>
 98. Patient-Centered Outcomes Research Institute (PCORI). Influencing the Culture of Research. Published 2020. Accessed May 10, 2021. <https://www.pcori.org/engagement/influencing-culture-research>
 99. Alston M, Ferro C, Muldoon LD, Pelizzari P. *Addressing Challenges in the Transition to Value-Based Care and Alternative Payment Models.*; 2017. https://www.milliman.com/-/media/products/bundled-payment-reporting-interface/addressing_challenges_transition_value_based_care_and_apms_20171207.aspx
 100. Butler S, Linnehan JE. More than half of health plans use outcomes-based contracts. Published 2019. Accessed April 20, 2021. <https://avalere.com/press-releases/more-than-half-of-health-plans-use-outcomes-based-contracts>



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