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# VALUE & OUTCOMES SPOTLIGHT

*A magazine for the global HEOR community.*

## VALUING FUTURE ALZHEIMER'S DISEASE TREATMENTS:

*The Need for a Holistic Approach*

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The mission of *Value & Outcomes Spotlight* is to foster dialogue within the global health economics and outcomes research (HEOR) community by reviewing the impact of HEOR methodologies on health policy and healthcare delivery to ultimately improve decision making for health globally.

**S3 Perspectives on Value Frameworks in Alzheimer's Disease**

Eric Jutkowitz and Joseph Gaugler

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*As we struggle with the rapidly growing challenge of Alzheimer's disease and dementia, there is an urgent need for robust and sustained responses in countries around the world. We are on the cusp of significant discoveries that may make it more manageable and give hope to millions. Discussions and decisions about value will play an important role in maximizing the benefits for people, families, and societies.*

**S7 Defining Elements of Value in Alzheimer's Disease**

Louis P. Garrison, Jr, Matthew Baumgart, Youssef H. El-Hayek, Drew Holzapfel, and Chris Leibman

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Paola Barbarino, Anders Gustavsson, and Peter J. Neumann

*There is a pressing need for payers, value assessors, and the broader Alzheimer's community to integrate real-world evidence into long-term value assessments. This paper examines the need for long-term evidence as an essential part of Alzheimer's value assessments, especially as disease-modifying therapies enter phase III trials.*

## Perspectives on Value Frameworks in Alzheimer's Disease

**Eric Jutkowitz, PhD**, Department of Health Services, Policy and Practice, Brown University School of Public Health, Providence Veterans Affairs Medical Center, Center of Innovation in Long Term Services and Supports, Providence, RI, USA; and **Joseph Gaugler, PhD**, Division of Health Policy and Management, School of Public Health, University of Minnesota, Minneapolis, MN, USA

Globally, 50 million people are living with Alzheimer's disease and related dementias (ADRD) and by mid-century, an estimated 152 million people will be living with ADRD.<sup>1</sup> ADRD disproportionately affects older people and women. In the United States, the prevalence of ADRD is nearly 2 times greater among Blacks and 1.5 times greater among Latinos compared to Whites.<sup>2</sup> People living with ADRD receive most of their care from family and friend caregivers.<sup>3,4</sup> Currently, there is no ADRD disease-modifying therapy on the market, but 80% of ADRD drugs in development are disease-modifying and 29 drug candidates are in phase III development.<sup>5</sup> There are also a number of nondrug interventions that have demonstrated statistically and clinically meaningful benefits for people living with ADRD and their caregivers, including improving quality of life.<sup>6,7</sup> Finally, there are a number of emerging diagnostic tests to identify ADRD earlier in the disease course.<sup>6</sup> Despite scientific advances in improving ADRD care, reimbursement of ADRD interventions has been stymied by value assessment frameworks not equipped to evaluate the effects of these therapeutics on the complex epidemiology of ADRD. In this supplement of *Value & Outcomes Spotlight*, 3 contributors provide perspectives on modifying value frameworks to evaluate current and emerging ADRD interventions.

Decision makers use value assessment frameworks to allocate resources. Many high-income countries have formal value assessment frameworks to determine the funding of healthcare programs. The United States is a notable exception, with a fragmented payer system. Each payer makes its own funding decisions. In a fragmented system, payers may have conflicting objectives and are not always transparent about how value is defined. In the first article, Garrison et al propose that funders should evaluate the value of an ADRD intervention from a wide perspective and draw on the "value flower" as a framework to evaluate ADRD interventions.<sup>8</sup> The value flower framework was developed as part of a 2018 ISPOR task force review of value frameworks.<sup>9</sup> Within the value flower framework, Garrison et al note the importance of domains related to productivity and distributional or equity considerations as particularly relevant to ADRD interventions. The lost productivity of people living with ADRD and their caregiver(s) is one of the largest cost drivers of ADRD, yet value frameworks that adopt a healthcare system perspective typically ignore productivity losses. Ignoring intervention effects, even if small, on productivity greatly underestimates the value of a therapy. The equity considerations include giving weight to an intervention that helps people with ADRD since it is a disease that disproportionately impacts older individuals, women, low-resourced communities, and Black, indigenous, and persons of color.

Building on Garrison et al, Basu et al focus on the brain equity considerations within a value framework and suggest using an equity-efficacy impact plane to evaluate ADRD interventions.<sup>10</sup> In an equity-efficacy framework, there is value in interventions that are less cost-effective treatments so long as they reduce health inequities. A challenge when considering the brain equity effects of an intervention is reconciling the multiple approaches to evaluate equity (eg, fair share approach, rights-based approach, moral rights). It is unclear how to weigh results from different but equally valid equity perspectives. Importantly, it is not just the fact that ADRD interventions can reduce inequalities, but there must be mechanisms in place to ensure all people living with ADRD can access treatment. For example, there are few neurologists in rural America, so this may impact the ability to diagnose and prescribe any new ADRD therapeutic.<sup>11</sup>

Although reimbursement and implementation decisions are not based on a single data point, a key metric in traditional value frameworks is cost per quality-adjusted life years (QALYs). Cost per QALY is also a metric in the value flower framework. Garrison et al and Basu et al note the challenges with using a cost per QALY framework to evaluate ADRD interventions. First, QALYs can be used in a way that places a lower value of life on older people. Second, many ADRD-related interventions yield benefits to the person with ADRD and their caregiver(s). Yet, QALYs are often only evaluated for either the person with ADRD or caregiver, but not both. This poses a challenge in a fragmented payer system like that of the United States, where the person with ADRD and their caregiver(s) may be beneficiaries of different insurance schemes. Third, standard health-related quality of life instruments may not fully capture the benefits of ADRD interventions. Finally, cost per QALY is concerned with maximizing total benefit and ignores the equitable allocation of resources.

The reality is that healthcare payers have budget constraints. Payers must not only navigate funding ADRD care but also must pay for interventions that help people with other costly chronic diseases. Emerging value and subscription payment models hold promise as a way to reimburse for innovative ADRD interventions that may have long-term value. Most value frameworks focus specifically on the initial adoption/funding decision, and have limited mechanisms for evaluating value over time. ADRD is a neurodegenerative disease, and people can live many years with ADRD. Interventions may have long-term effects, but clinical trials of ADRD interventions are only conducted for relatively short time periods. A common theme in all the articles is the need to assess the long-term value of an ADRD intervention.

Barbarino et al identify data gaps that must be addressed to evaluate the long-term value of ADRD interventions.<sup>12</sup> First, many of the emerging ADRD therapeutic candidates will most likely be effective in the early stages of cognitive impairment; yet, payment and clinical policies do not support early screening efforts. Without early detection efforts, we may not be able to identify people who would benefit most from emerging disease-modifying therapeutics. Second, we must better understand the effect of interventions on outcomes (eg, quality of life, independence, productivity) that are meaningful to patients, caregivers, health systems, and society at large using validated measures. Meaningful ADRD-related measures are not systematically collected in administrative data or clinical practice, but they are what people care about and could be used to evaluate the long-term value of an ADRD intervention. Notable examples of incorporating meaningful ADRD outcomes include the application of goal attainment scaling in the context of multidisciplinary, collaborative dementia care models.<sup>13</sup>

## Conclusions

Multiple ADRD therapeutics are in development and may come to market within the next decade. ADRD affects people living with the disease, family/friends, healthcare systems, communities, and society. The value of an intervention likely will vary across these entities. While the societal benefits of an ADRD intervention may be large, all stakeholders or payers may not obtain equal returns. Traditional value frameworks that rely on a cost per QALY approach and a narrow stakeholder perspective are not suited to the unique challenges of ADRD. Value frameworks, which incorporate multiple perspectives, health/brain equity considerations, and long-term evaluation are needed. Innovation in the systematic collection of meaningful ADRD outcomes will facilitate the adoption of new interventions. There have been tremendous scientific advances in improving ADRD care. It is now time for value frameworks and payment systems to catch up. •

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# The Essential Role of Value Assessment in Addressing the Global Dementia Crisis

Paola Barbarino, MA, Chief Executive Officer, Alzheimer's Disease International, London, England, UK

As people, families, and societies struggle with the rapidly growing challenge of Alzheimer's disease and dementia, there is an urgent need for robust and sustained responses in countries around the world, ranging from risk reduction to early diagnosis to postdiagnostic support, interventions, and care. Leaders and experts must collaborate across sectors to chart a path forward, especially given the potential for new dementia treatments, diagnostics, and interventions.

Value assessment is fundamental to ensuring these efforts deliver the support that people and families need. Only by building consensus on how to appropriately assess value in dementia can we ensure that new advances reach all who need them. To inform this discussion, the pieces in this supplement provide perspectives from leading experts in the field: the first piece frames the core issues, elements, and questions of value assessment<sup>1</sup>; the second applies the lens of health equity<sup>2</sup>; and the third considers the need for long-term value demonstration.<sup>3</sup> All 3 of these topics are critical as stakeholders work together to improve care, find a cure, and, most importantly, ensure that all people and families affected by dementia receive the support they need.

## The Need for Investment in Dementia Has Never Been Greater

The past year has illustrated the importance of investing in strong, sustained, and proactive responses to global health challenges, such as Alzheimer's disease and dementia. The COVID-19 pandemic has exposed the huge cost of governments' underinvestment in health and care systems—in low-, middle- and high-income countries, alike. People with dementia have been especially vulnerable, both in terms of the high mortality associated with COVID-19 and in dealing with social isolation, as well as through the closing of services across the health continuum. COVID-19 also offers an important comparison for the global dementia crisis, which must be met with similar levels of urgency, coordination, and investment.

At Alzheimer's Disease International (ADI), the global federation of Alzheimer associations, we see the impact of COVID-19 on dementia diagnosis as especially concerning. As COVID-19 spread, people were understandably reluctant to visit clinics and seek help for early signs of cognitive impairment, as many of the members of our Medical and Scientific Advisory Panel reported early in the pandemic. These impacts now threaten to exacerbate the long-standing challenges in dementia diagnosis, which are at the heart of the dementia crisis.

As a result, there is a need for greater focus and investment to enable early diagnosis, postdiagnostic support, and appropriate care and interventions. Currently, there is a lack of the necessary skill and equipment for diagnosis, such as

positron emission tomography (PET) scanners, which are prohibitively expensive. There is also a shortage of experts like gerontologists, psychiatrists, and neurologists, especially in low- and middle-income settings. Further, a 2017 OECD report revealed that fewer than 40% of OECD countries were able to estimate national dementia diagnosis rates and that many primary care doctors received less than 12 hours of dementia training.<sup>4</sup> Additionally, ADI's own research shows that 62% of healthcare practitioners, globally, perceive dementia to be a part of normal aging, rather than a condition requiring diagnosis and treatment.<sup>5</sup> There is also currently no simple, practical, and scalable blood biomarker test, although there have been some promising developments towards this end.<sup>6</sup>

Given these challenges, it is perhaps unsurprising that as few as 10% of those living with dementia in low- and middle-income countries receive a formal diagnosis. Even in higher income countries, only around half of individuals receive a diagnosis. And in all countries, lack of access to postdiagnostic support, treatment, and care generates significant barriers to living well.<sup>7</sup>

Therefore, stakeholders must collaborate and invest to improve diagnostic capacity, postdiagnostic support, and other critical elements of the response to Alzheimer's disease and dementia. A stronger, coordinated response would allow the millions of people impacted by dementia—including not only the more than 50 million people living with dementia, but also their families and loved ones—to better manage their condition, plan ahead, organize care needs, and access postdiagnostic support services. Early detection also allows people with Alzheimer's disease and dementia and their families to feel well-prepared and supported, alleviating initial feelings of shock, anger, and grief and providing a sense of reassurance and empowerment.<sup>5</sup> Moreover, there is a need to enable early intervention, which can delay the need for formal care, reducing total direct costs and burden, as well as potentially mitigating indirect costs like lost productivity and the impact of caregiving on mental health and well-being.<sup>5</sup>

## Leaders, Experts, and Stakeholders Must Build Consensus on Value Assessment

To address these challenges, policy makers, payers, and other stakeholders must discuss how to appropriately assess the value of diagnostics and interventions for Alzheimer's disease and dementia. This will be doubly important when new Alzheimer's disease treatments enter the market. Most prospective drug treatments currently being researched would require diagnosis in the earliest stage (the "prodromal" stage, also called mild cognitive impairment). Signs and markers at the prodromal stage provide valuable information, insights, and potentially an opportunity for intervention—either treatment or risk reduction.

Efforts that realize this potential could deliver significant benefits, as indicated by evidence on dementia's current burden across society. Globally, dementia generates total costs of \$1 trillion annually, and this cost will double in the next decade.<sup>8</sup> Informal care makes up 40% of this total cost, with the social care sector also shouldering an enormous 40%, and the medical sector the remaining 20%.<sup>9</sup> Stronger responses and interventions can help to mitigate these costs, as well as improve health equity for older people, vulnerable populations, and other key groups.

Further, social support for informal carers is currently lacking, often leading to additional impacts, costs, and burden. Our research shows that more than 50% of carers globally experienced poor health, including mental health, as a result of their caring responsibilities.<sup>5</sup> Improving the support services offered to carers is an expensive task, and while this should be a policy priority for all governments, this should also provide evidence to policy makers and payers of the benefit of investing in early detection and intervention. Governments should prioritize data-sharing and harmonization, engaging in initiatives like the World Health Organization's Global Dementia Observatory. This will assist in demonstrating long-term

value, including consensus on outcomes, data, and modeling. Additionally, there is a pressing need for payers, value assessors, and the broader Alzheimer's community to integrate real-world evidence into long-term value assessments.

The COVID-19 pandemic has shown the capacity for world leaders to find solutions to health challenges when the pressure to do so is great enough. As a matter of equity, governments must invest in dementia responses, and both governments and payers must be primed for a disease-modifying therapy. The economic and social costs of inaction are colossal.

Dementia is rapidly growing around the world. We are on the cusp of significant discoveries that may make it more manageable and give hope to millions. Discussions and decisions about value will play an important role in maximizing the benefits for people, families, and societies. It is our collective responsibility to ensure that there will be viable solutions in our future. We at ADI will continue to advocate for care for today and cure for tomorrow, but that tomorrow may be just around the corner. We cannot afford inaction. ●

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## Defining Elements of Value in Alzheimer's Disease

Louis P. Garrison, Jr, PhD, Department of Pharmacy, University of Washington, Seattle, WA, USA; Matthew Baumgart, Vice President, Health Policy, Alzheimer's Association, Chicago, IL, USA; Youssef H. El-Hayek, PhD, MBA, Senior Consultant, Shift Health, Toronto, Ontario Canada; Drew Holzapfel, MBA, Executive Director, The Global CEO Initiative on Alzheimer's Disease, Washington, DC, USA; Chris Leibman, PharmD, MS, Senior Vice President, Value and Access, Biogen, Cambridge, MA, USA



### The Importance of Value Assessment in Alzheimer's Disease

Alzheimer's disease presents one of the greatest health, economic, and societal challenges of our time. The global community has now reached a critical point in our response to this challenge, as decades of scientific research will likely soon deliver the first disease-modifying Alzheimer's therapies. This inflection point generates an urgent need for greater discussion and consensus on how to assess the full value of new Alzheimer's therapies. This discussion, and the resulting decisions by value assessors, policy makers, and other stakeholders, will play a fundamental role in shaping long-term responses to Alzheimer's disease in countries around the world.

The stakes are high. Alzheimer's disease and dementia are grave and growing threats with dramatic impacts on people, families, communities, economies, and societies around the world. Prevalence is projected to roughly triple from more than 50 million in 2019 to around 152 million by 2050.<sup>1</sup> This growing prevalence also brings immense rising costs, currently estimated at \$1 trillion and projected to double by 2030.<sup>1</sup> Yet even this dramatic figure may actually *understate* the societal and economic burden of Alzheimer's disease, given its complex impacts and hidden costs.

**Alzheimer's disease and dementia are grave and growing threats with dramatic impacts on people, families, communities, economies, and societies around the world.**

Against this backdrop, new disease-modifying Alzheimer's therapies offer the potential to change the course of both individual patient's disease progression and the global Alzheimer's crisis. While therapeutic progress has been slow in recent decades, there are now currently 29 candidates in phase III clinical development.<sup>2</sup> Further, 80% of all candidates (across all phases of development) are disease-modifying therapies, representing a potential step-change to treatment.<sup>2</sup> New disease-modifying therapies may finally be available to those with Alzheimer's disease in the next several years.

Value assessments and decisions will shape the real-world impact of these therapies. Therefore, now is the time for value assessors, policy makers, the medical and advocacy

communities, the private sector, and other key stakeholders to engage in greater dialogue about how the value of a treatment can best reflect the full scale of the Alzheimer's challenge.

While traditional value frameworks provide an important starting point, Alzheimer's disease presents a uniquely complex and widespread burden—and resulting potential for therapeutic value—that is not fully captured by current frameworks. This is a progressive disease that grows worse over many years; places an immense strain on caregivers' and families' health, finances, and productivity; and generates a number of direct and indirect costs for health and long-term care systems, economies, and society. However, traditional value frameworks do not fully capture these considerations.

To advance the Alzheimer's value dialogue, this article provides an overview of forward-looking approaches and diverse perspectives from academia, policy and advocacy experts, and industry. It adds to the value discussion by examining several key topics:

- Considerations beyond cost per QALY (quality-adjusted life years) and the novel elements of value in the ISPOR value flower (Figure 1)
- Patients' and caregivers' perspectives on the real-world outcomes that are most meaningful to them
- The "hidden" costs of Alzheimer's disease for patients, caregivers, families, health systems, economies, and society overall
- How recent research findings and the need for continuous innovation can inform value discussions and decisions.

We hope the article sparks greater discussion of value in Alzheimer's, including the full range of costs and impacts from the disease, the lived experience of patients and caregivers, and the cutting edge of medical science. Ultimately, this more nuanced perspective can help to ensure key value decisions are aligned with the urgency of the Alzheimer's challenge and the needs of those most directly affected.

### The Value Flower: Extending the Value Paradigm

Alzheimer's disease presents challenges to typical cost-effectiveness frameworks, which for decades have centered on QALYs and net cost. QALYs assess a treatment's benefits based on the narrow criteria of length of life and quality of life, while net cost considers the treatment's direct medical costs and

the healthcare savings it provides. Together, these 2 elements lead to cost per QALY, which serves as a flexible and convenient metric for measuring and comparing health outcomes across diverse diseases and treatment.

However, in recent years, there has been significant concern about whether the cost per QALY model is appropriately suited to certain disease areas, including Alzheimer's. This framework includes paid patient costs and benefits but omits a range of opportunity costs. Further, in Alzheimer's disease, the patient typically becomes dependent on the caregiver for their everyday functioning, which makes the burden on the caregiver an essential aspect of the disease. However, this burden is currently excluded from traditional cost-effectiveness frameworks, which also do not fully capture the burdens on families, economies, and society.

Given these gaps, it may be necessary to expand the cost per QALY framework to include new elements of burden and value, or to develop a novel framework that is better suited to these dynamics. In 2018, an ISPOR task force group reviewed a number of alternative frameworks and synthesized an overarching approach, often referred to as the value flower.<sup>3</sup> The value flower “broadens the view of what constitutes value in healthcare” with 10 elements that extend beyond traditional cost per QALY analysis (Figure 1). Several of these elements of value are especially relevant to Alzheimer's disease.

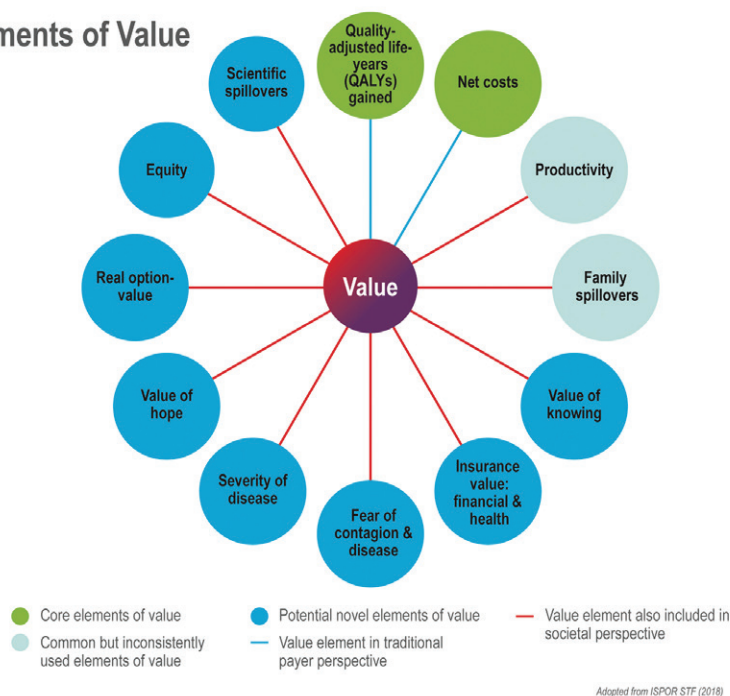
**In Alzheimer's disease, the patient typically becomes dependent on the caregiver for their everyday functioning, which makes the burden on the caregiver an essential aspect of the disease.**

Productivity measures the impact on patients' and caregivers' ability to work, both at home and in the labor market. As caregivers often work less or drop out of the workforce altogether, lost productivity adds to the total costs of the disease. This results in an immense financial and economic burden on caregivers, families, and societies, yet the potential value of reducing these impacts is not included in the traditional cost per QALY approach.

The concept of “scientific spillover” measures the value of scientific research that advances the overall field, regardless

**Figure 1: Elements of value in the value flower.**

### Elements of Value



of direct resulting health benefit. For example, basic science or clinical trial results may not lead to an approved therapy that directly benefits patients, but they can contribute to the overall body of knowledge in Alzheimer's disease.

“Family spillovers” measures the “disutility” (ie, harmful physical and mental effects of Alzheimer's disease) on caregivers and family over a period of time. This is especially relevant given research that finds caregivers of Alzheimer's patients face greater health impacts and higher healthcare costs.<sup>4</sup>

A number of the value flower's elements focus on the value of reducing uncertainty. The “value of knowing” measures the benefits of being more certain about the patients for which a specific treatment or intervention will be effective (eg, a blood test). The “insurance value” measures the value of increasing people's financial protection from the costs of Alzheimer's. “Fear of contagion” measures the value of reducing people's fear of developing Alzheimer's disease and having no effective treatment options.

“Distributional equity” measures the value of addressing the disproportionate impacts of Alzheimer's disease on different groups and communities, including based on gender, racial and ethnic identity, socioeconomic status, and educational level. It could also include the value of greater equity between people who develop Alzheimer's and those who do not develop it. This element of value is explored in greater detail in the article by Basu et al in this supplement.<sup>5</sup>



While further work is needed to determine which of these elements are most important in Alzheimer's disease and how they can be measured, the value flower provides a core framework to consider how a potential Alzheimer's therapy can benefit patients, caregivers, and society overall, especially beyond traditional cost per QALY.

### The Perspective of Patients and Caregivers: Defining Meaningful Real-World Outcomes

Recent research has attempted to better understand the real-world needs and priorities of those most directly affected by Alzheimer's disease. Together with the value flower, this research provides the basis for a broader range of value considerations—grounded in meaningful outcomes for patients and caregivers.

A systematic review, conducted on behalf of the Real-World Outcomes Across the Alzheimer's Disease Spectrum: A Multimodal Data Access Platform (ROADMAP) initiative, examined 34 relevant studies to better understand the priorities of Alzheimer's patients, caregivers, and healthcare providers in countries around the world. The review found patients and caregivers value a range of key priorities that are not typically included in clinical trials or value discussions, such as independence and identity.<sup>6</sup> Notably, these priorities are consistent across different studies, geographies, and patients and caregivers.

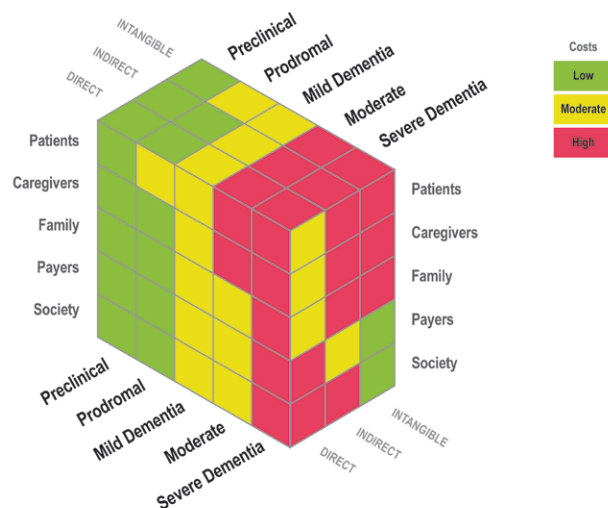
**As the primary beneficiaries of new Alzheimer's therapies, patients' and caregivers' perspectives must ground decisions about value.**

Of the 34 studies included in the systematic review, the most frequently reported important outcomes included maintaining a patient's independence, including both physical and psychological autonomy; mental health impacts, such as anxiety and depression, with spousal caregivers noting that targeting depression is critical; and the ability of patients to maintain their identity, including knowledge, personality traits, and emotional bonds.

Overall, this research finds that those most directly affected by Alzheimer's disease are primarily concerned with observable effects on their daily life. Therefore, a therapy's ability to mitigate or delay the negative impacts of Alzheimer's on these areas is its greatest source of value in the view of patients and caregivers—more so than the raw clinical measurement of biomarkers or an abstract cognitive test score. While these measures can serve as important proxies, patients and caregivers are ultimately focused on the impacts for how they feel, live, interact, and see themselves every day.

The Alzheimer's Disease Patient and Caregiver Engagement (AD PACE) What Matters Most (WMM) study provides further evidence to support these findings. The WMM study conducted qualitative interviews with patients and caregivers across 5 groups, from

Figure 2: The hidden costs of Alzheimer's.



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individuals with higher risk or underlying pathology but no symptoms to caregivers of those with severe Alzheimer's disease.<sup>7</sup>

Of 42 concepts whose importance was assessed by the WMM study, all were rated by at least half of patients as very important or extremely important, indicating that those living with dementia have a broad and diverse set of priorities and concerns. Caregivers had a narrower set of concepts they considered important, but both agreed on the importance of concepts linked to emotional well-being, such as not feeling down and depressed, not feeling anxious, and having a sense of purpose. These were rated as more important than more "practical" concepts like remembering people's names or learning new information and tasks.

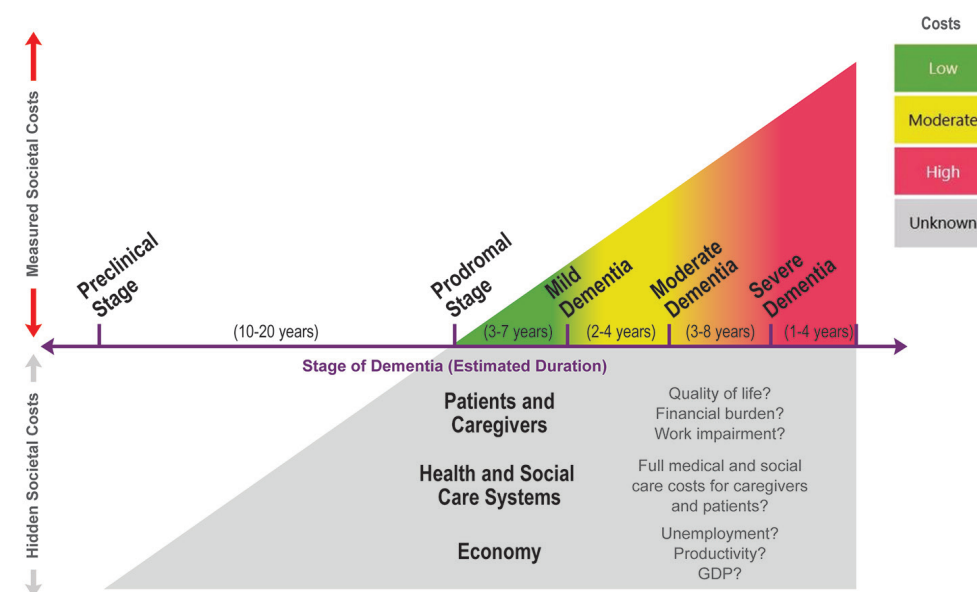
As the primary beneficiaries of new Alzheimer's therapies, the patients' and caregivers' perspectives must ground decisions about value. Initial research reveals a broad set of everyday priorities, many of which are not currently integrated into traditional value frameworks. Further work is needed to determine how best to measure these priorities in a way that is consistent and easy to incorporate when assessing value for specific therapies.

### Financial, Economic, and Societal Burden: Examining the "Hidden Costs" of Alzheimer's

Due to its impacts on patients and caregivers, Alzheimer's disease leads to cascading costs for both those directly affected and society more broadly. Dementia is generally recognized as one of the most expensive health challenges of our time, generating roughly \$1 trillion in costs (or greater than 1% of global gross domestic product [GDP]).<sup>8,9</sup>

However, given the nature of the disease, these costs can be hidden (ie, spread across health systems, long-term care systems, and payers; paid by families out of pocket; attributed to comorbid conditions, etc), creating an invisible drain on the workforce and beginning even before diagnosis (Figure 2).<sup>10</sup>

Figure 3: The costs of dementia steadily increase, beginning before diagnosis.



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“Tip of the Iceberg: Assessing the Global Socioeconomic Costs of Alzheimer’s Disease and Related Dementias and Strategic Implications for Stakeholders” by El-Hayek et al provides the framework for a more comprehensive analysis of these costs, which could help to better align the value of therapies with the true burden of Alzheimer’s disease and the potential savings of new therapies. The piece finds that the frequently measured costs of Alzheimer’s are only the “tip of the iceberg,” missing both certain *types* of costs (eg, out-of-pocket, lost productivity, etc) as well as a certain *time* (eg, costs that occur before diagnosis) (Figure 3).<sup>10</sup>

The authors outline the costs of Alzheimer’s disease in 3 categories: (1) direct costs, (2) indirect costs, and (3) intangible costs. Direct costs include medical costs such as medication and hospitalization, along with social or elder care costs such as long-term residential care. Direct costs begin even before Alzheimer’s diagnosis and steadily increase over time. They include out-of-pocket spending, which is high relative to the spending of those without the disease and “disproportionately borne by women and minorities.” Hidden direct costs may also include the higher costs of comorbidities for Alzheimer’s patients and caregivers.

Indirect costs constitute a less visible but similarly heavy burden. These include the cost of uncompensated caregiving, nearly \$244 billion in the United States in 2019.<sup>11</sup> These also include productivity losses, as well as the financial impact on caregivers’ income and savings. Indirect costs may also accrue for years prior to a diagnosis, yet they also increase during the Alzheimer’s journey as the disease reduces patients’ autonomy and self-sufficiency.

Finally, intangible costs are those that burden patients and family members in ways that are difficult to measure in financial

terms. These types of costs include the reduced quality of life experienced by people with Alzheimer’s disease and their caregivers.

Given these considerations, the research community needs additional consensus, tools, and data to measure and understand the full real-world costs of Alzheimer’s disease. For example, new technology, such as apps or wearables, could possibly measure time spent on caregiving, and new biomarker tests could enable earlier diagnoses and thus detect changes and costs earlier in disease progression. Value assessment can also benefit from observational studies and registries that measure disease-related burdens “across the continuum of aging, cognitive impairment, and dementia.”

### The Value of Innovation: Evolving Value Assessment to Reflect the Current State of Alzheimer’s Science

In addition to the considerations above, determining the value of Alzheimer’s therapies must evolve to reflect the latest science on Alzheimer’s disease. In the past 2 decades, researchers, the medical community, and the private sector have achieved important strides to better understand Alzheimer’s disease and develop new interventions. This is a journey of progress, enabling the scientific community to possess a deeper understanding of Alzheimer’s, how to identify and target the disease in its earliest stages, and how to account for its heterogeneity. With a record 29 drug candidates in phase III clinical development—59% of which are disease-modifying therapies—the future now looks brighter than ever.<sup>2</sup>

However, since therapeutic progress has been slow, value assessors and payers have not kept pace with the latest scientific findings. As a result, it is now time to update value frameworks

to reflect the cutting edge of Alzheimer's science and innovation. This alignment offers the greatest opportunity to ensure the right patients receive the right therapies at the right time to achieve the best outcomes.

Several key findings are essential. Early detection, diagnosis, and intervention are critical to both preserve the real-world outcomes that matter to patients and bend the long-term cost curve for society. A given therapy will likely achieve the greatest value in patients in the mild stage of Alzheimer's or with mild cognitive impairment. Value frameworks should reflect these considerations, ensuring that the right patients can receive a therapy early enough to maximize its benefits, savings, and overall value.

Researchers now also have a greater understanding of how Alzheimer's disease ripples across society. These impacts and costs are not captured in one "budget," but spread across households, health systems, long-term care systems, payers, communities, economies, and more. Together, these costs represent one of the most expensive healthcare challenges in our world, and this should be reflected in valuing new therapies.

Finally, new therapies will likely change the dynamics of how Alzheimer's disease is detected, diagnosed, and discussed, while also stimulating new innovation. Any successful therapy will affect all other innovation efforts, driving further progress; others can learn from and build upon a breakthrough. Therefore, value frameworks must continuously evolve to capture and reflect these changes.

## New Directions in Value Assessment for Alzheimer's Disease

There is clear and urgent need for innovative approaches that more accurately and appropriately evaluate the full benefits and savings of new therapies for Alzheimer's disease. Though the area is ripe for further research, existing scholarship offers several primary takeaways:

- The unique nature, challenges, and impacts of Alzheimer's disease require expanding the value discussion beyond traditional cost per QALY, incorporating additional considerations or turning to novel frameworks like the value flower.
- Patients and caregivers prioritize meaningful, but sometimes intangible real-world outcomes, such as the preservation of independence, emotional well-being, and identity.
- The costs of Alzheimer's disease are hidden across multiple systems and stakeholders, and they begin to accrue years before diagnosis.
- Maximizing the value of new therapies likely requires intervening early in disease progression and identifying the right subpopulations of patients.
- Value assessment in Alzheimer's disease can evolve to reflect new scientific findings and innovations, and then continue to evolve in the future.

The next 2 articles in this supplement provide additional detail about these and other aspects of value in Alzheimer's disease.<sup>5,12</sup> We look forward to engaging the Alzheimer's community, value assessors, and policy makers in further discussions about how to integrate these considerations into value decisions and ultimately accelerate our world's response to Alzheimer's disease. •

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## Value Assessment in Alzheimer's Disease: A Focus on Equity

Anirban Basu, PhD, MS, Department of Health Economics, University of Washington School of Pharmacy, Seattle, WA, USA; Nancy Lynn, MA, Senior Vice President, Strategic Partnerships, BrightFocus Foundation, Los Angeles, CA, USA; Susan Peschin, MHS, President and CEO, Alliance for Aging Research, Washington, DC, USA; Jason Resendez, Executive Director, UsAgainstAlzheimer's Center for Brain Health Equity, Washington, DC, USA



### Equity as an Essential Value Consideration

The hardship of Alzheimer's disease is not only immense—but highly unequal. The disease's health and economic consequences fall disproportionately on certain demographics, including older adults, women, people of color, and those with lower levels of education and wealth.

Given these disparities, one of the main benefits of a novel disease-modifying Alzheimer's therapy would be its potential to improve health equity. Yet this potential is not considered in traditional value assessment frameworks. With several Alzheimer's therapies in phase III clinical trials, now is the time to consider how value assessments can incorporate elements to reflect the value of making society more equitable, ethical, and inclusive. These elements could be included alongside traditional cost-effectiveness metrics to inform deliberative processes on value decisions, leading to more robust deliberation that fully captures key considerations like equity.

The inequities of Alzheimer's disease and other dementias can be traced across demographic lines. Most evidently, Alzheimer's disease disproportionately affects older adults. In the United States, 10% of Americans 65 years or older—or 5.8 million people—live with Alzheimer's disease, and, within that group, prevalence rates increase with age.<sup>1</sup> Overall, 80% of Americans living with Alzheimer's disease are 75 years old or more.<sup>1</sup>

Racial disparities in Alzheimer's disease are also stark. Older Black Americans are approximately twice as likely to have Alzheimer's disease or a related dementia as older White Americans, while older Latinos are about 1.5 times more likely.<sup>1</sup> Many factors contribute to this disproportionate prevalence. Black and Latino populations have higher rates of risk factors like cardiovascular disease and diabetes, as well as socioeconomic risk factors like lower levels of education, higher rates of poverty, and greater exposure to discrimination.<sup>1</sup>

Alzheimer's disease also has an outsized impact on women. Two-thirds of Americans with dementia are women, and a woman has about a 20% chance of developing the disease during her lifetime.<sup>2</sup> A man, however, only faces about a 10% risk over the course of a lifetime.<sup>2</sup> And two-thirds of caregivers (spouses or children) are women, providing the vast majority of the 18.6 billion hours of unpaid dementia care in the United States, valued at almost \$244 billion.<sup>1</sup> Many of these women must also care for children, as part of the “sandwich generation,” and many reduce their work hours or drop out of the workforce altogether because of these care responsibilities.<sup>3</sup>

Even with these stark demographic trends, traditional value assessment frameworks do not account for inequities or the potential for new therapies to promote health equity. This is a missed opportunity. Widespread access to an effective disease-modifying therapy has the potential to reduce the disproportionate impact on women of all ages, communities of color, and older adults. The benefits of an innovative treatment to these demographic groups should not be overlooked.

This paper explores how equity considerations could be better integrated into value assessment frameworks by examining several key topics:

- The limitations of traditional value assessment and QALYs, as seen through an equity lens
- The growing and disproportionate impact of Alzheimer's disease on women and Black and Latino communities, the barriers to “brain health equity,” and the importance of addressing racial inequities
- Different perspectives on what equity means for an eventual disease-modifying Alzheimer's treatment
- Real-world impacts and potential new models to better incorporate equity into future Alzheimer's value assessments, deliberations, and decisions

The goal of this article is to spark discussion about health equity in value assessment. Value frameworks must better reflect health equity to not only enhance the benefits of new Alzheimer's treatments, but also protect the most vulnerable people in our society.

### The Challenges of Equity: QALY Controversies, Distributive Justice, and Incomplete Valuation

As discussed in the first piece of this supplement, quality-adjusted life years (QALYs) are the traditional metric for cost-effectiveness analyses (CEA) within value assessment.<sup>4</sup> Cost-per-QALY analyses are used to compare the value of treatment options among different disease areas and guide decisions about how to allocate resources, when considering a desire for a framework to equate conditions and resources and facilitate “objective” decision making. The best return on investment can be considered as the most favorable cost per QALY. However, when viewed through a lens of equity, QALYs have been criticized because they can be used in a way that effectively discriminates against older, sicker patients in evaluating treatments that extend life expectancies. Additionally, like any other single health outcomes metric, cost per QALY, by itself,



cannot and does not advance distributive justice and overlooks the functional benefits of better health.

First, cost-per-QALY evaluations effectively place a lower value on the lives of certain patients, especially those who are older or living with comorbid conditions. A QALY measures both the length and quality of life that a health technology will provide to a patient. Therefore, people living with comorbidities or a disability, as is common in older patients, are assigned a lower initial quality of life in the QALY framework, which effectively places a lower value on extending their lives compared to a younger, healthier patient who experiences the same gains in life expectancy.

Second, cost-per-QALY evaluations only consider the utilitarian principle of maximizing total benefit. It leaves out many other questions of distributive justice, which concerns the equitable allocation of resources. For example, cost per QALY does not consider the size of the population represented by the condition or intervention and is unfit to address questions of whether it is better to provide large benefits to a small number of people, or small benefits to a large number of people. Further, it does not support examinations of the value that should be placed on benefiting groups that have been historically marginalized and under-served. These are the difficult questions of distributive justice. Answering them requires carefully weighing societal values, priorities, and needs. But traditional value assessments do not have a clear mechanism to answer these difficult questions.

Third, cost-per-QALY evaluations do not capture a treatment's functional benefits beyond lifespan and quality of life, raising concerns about incomplete valuations. For example, a treatment can have productivity benefits by enabling patients and caregivers to stay in the formal workforce, do productive work in their household, volunteer in their community, or provide other forms of value to society. In the case of cognitive decline, an effective treatment could provide broader benefits for a patient's quality of life that are not captured in standard health-related quality of life instruments. However, these functional benefits are not measured by typical cost-per-QALY evaluations. Moreover, a treatment that slows the progression of Alzheimer's disease can have important quality of life benefits for caregivers, reducing physical, emotional, and financial strains.

To address these concerns, supplements and alternatives to QALYs have been developed. The Institute for Clinical and Economic Review (ICER) has proposed a secondary measure, the Equal Value of Life Years Gained (evLYG) metric.<sup>5</sup> The evLYG values all life years gained equally, regardless of the patient's starting quality of life. However, this also means that the evLYG metric can undervalue treatments that improve quality of life.

Another alternative is health years in total (HYT), developed by researchers at the University of Washington. Under this metric, a treatment's life expectancy effects are added to its quality-of-

life effects.<sup>6</sup> By taking this additive approach, rather than the multiplicative approach that characterizes QALY analysis, HYT analysis avoids the devaluation of patient life years that occurs when utility weight is multiplied by life years. In doing so, the HYT framework leads towards more equitable outcomes for patients with lower quality of life, enabling them to fully benefit from therapies that increase life expectancy.

Finally, despite the criticisms of CEA and QALYs, it should be noted that such analyses can be effective if employed as one consideration among many. Indeed, no guideline or recommendation that calls for the use of CEA states that CEA should be the sole factor on which such resource allocation decisions are made. CEA results can be included in a broader set of metrics and perspectives that inform a deliberative process's ultimate decisions. Many of the criticisms of CEA can be addressed through such deliberative processes, which could include metrics on health equity and other key elements of value, as well as perspectives shared by those who are most directly and disproportionately affected by Alzheimer's disease.

### **Barriers to Brain Health Equity: The Unequal Impacts of Alzheimer's Disease on Women and Communities of Color**

Since value assessment frameworks are a tool developed to help payers allocate resources to achieve socially desirable goals, value assessors must clearly define their goals and values. One of these goals should be "brain health equity" (ie, the same opportunity for brain health, regardless of race, gender, ethnicity, socioeconomic status, or other demographic factors). Our society is far from achieving this goal, particularly given the disproportionate impacts of Alzheimer's disease on women and racial and ethnic minorities. As stated previously, women account for a majority of the people with Alzheimer's disease, provide a disproportionate share of Alzheimer's care, and bear a severely unequal financial cost, as both patients and caregivers. Of the 5.8 million Americans 65 years and older who live with Alzheimer's disease, 3.6 million—almost two-thirds—are women.<sup>1</sup> Several factors may contribute to this greater prevalence, including longer lifespans, genetic differences, and levels of educational attainment.<sup>1</sup>

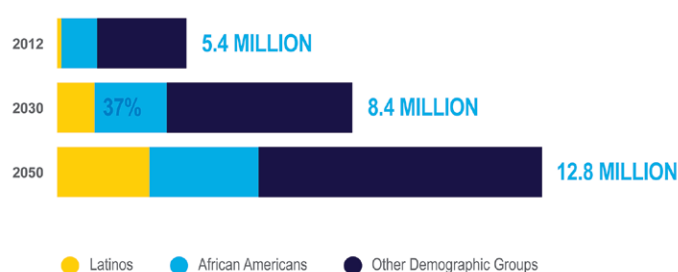
In the United States, approximately two-thirds of Alzheimer's caregivers are also women, with daughters comprising approximately one-third of caregivers.<sup>1</sup> Women who are caregivers also spend more time on care, as 73% of dementia caregivers who provide more than 40 hours of care per week are women, and 2.5 more women than men live full-time with a person with dementia.<sup>1</sup> Even more troubling, approximately one-quarter of dementia caregivers belong to the "sandwich generation," caring for one or more aging parents while taking care of children under 18 years old.<sup>1</sup> These heavy caregiving responsibilities often have a significant, complex impact on women. Approximately 19% of women who care for loved ones with Alzheimer's disease had to quit work to manage their caregiving responsibilities.<sup>7</sup> Women caregivers have been found



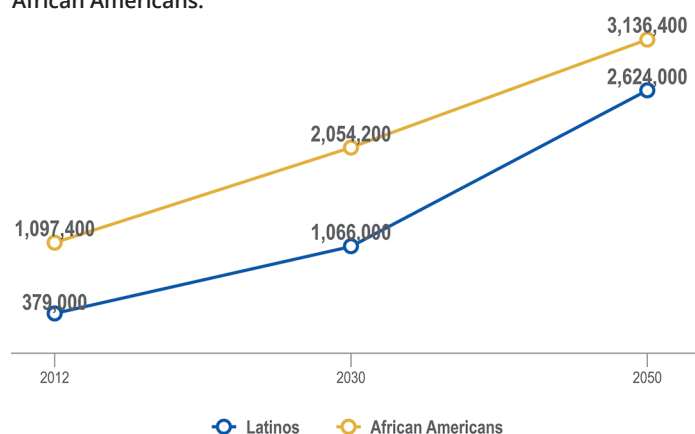
to experience higher levels of depression, impaired mood, and negative health outcomes than male caregivers.<sup>1</sup>

Women also bear a disproportionate share of the direct and indirect costs of Alzheimer's disease. The cumulative direct cost of treating women with dementia in the United States from 2012 to 2040 is estimated at around \$370 billion, or approximately 70% of cumulative direct costs.<sup>7</sup> Indirect costs, such as reduced productivity and workforce participation, associated with women are projected to reach approximately \$2.1 trillion between 2012 and 2040, making up approximately 80% of cumulative indirect costs.<sup>8</sup>

**Figure 1: By 2030, nearly 40% of Americans living with Alzheimer's disease will be Latino or African American.**



**Figure 2: Alzheimer's disease prevalence among Latinos and African Americans.**

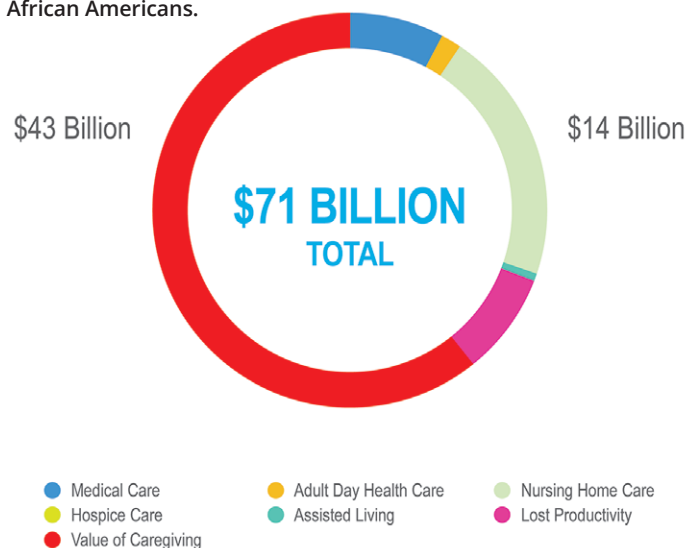


Racial and ethnic disparities are also stark. In the United States, Black and Latino communities account for a growing share of the Alzheimer's patient population. According to Florida International University and UsAgainstAlzheimer's, by 2030, nearly 40% of people living with Alzheimer's disease and related dementias will be Latino or African American (Figure 1).<sup>9</sup>

The number of Black Americans living with Alzheimer's disease is expected to almost double from nearly 1.1 million in 2012 to over 2 million in 2030, and the number of Latinos with the disease is expected to nearly triple from 379,000 to around 1.1 million in the same period.<sup>9-11</sup> By 2050, these totals will continue to rise to over 3.1 million African Americans and 2.6 million Latinos (Figure 2).<sup>1,10</sup>

This growing prevalence translates into potentially debilitating costs for these communities, which already face severe socioeconomic disparities. Significantly, much of this cost is indirect, such as caregiving and lost productivity or lost wages, which is not captured by traditional value assessment (Figure 3). For example, in 2012, direct and indirect costs of Alzheimer's disease for African Americans totaled over \$71 billion. In particular, the cost of unpaid caregiving provided by African Americans accounted for more than \$43 billion—or approximately 60% of the total cost.<sup>10</sup> This economic burden is also geographically concentrated, with 49% of costs accruing in the American South.<sup>10</sup>

**Figure 3: Total direct and indirect costs of Alzheimer's disease on African Americans.**



If prevalence continues to grow on its current course, so will the economic burden. For Latinos, total direct and indirect costs are projected to steadily rise from approximately \$11 billion in 2012 to approximately \$30 billion in 2030 and \$105 billion in 2060 (Figure 4).<sup>11</sup> Again, indirect costs account for a significant share of the total economic burden.

Furthermore, these estimates may understate the trends for Black and Latino populations, as they are less likely to have easy access to health systems and may therefore go undiagnosed and remain excluded from data collection. A lack of healthcare access also means that marginalized groups are under-represented in clinical trials. To measure the full promise of new treatments for Alzheimer's disease—and ensure they benefit diverse communities—clinical trials must better represent racial and ethnic minorities. These data gaps, together with the inequities identified in existing research, clearly show that significant efforts are needed to improve health equity related to Alzheimer's disease. While value assessment alone is insufficient to drive the necessary progress, incorporating equity considerations into these discussions and decisions can help our society to recognize and work towards the promise of brain health equity.

Figure 4: Total direct and indirect costs of Alzheimer's disease on US Latinos nationally.

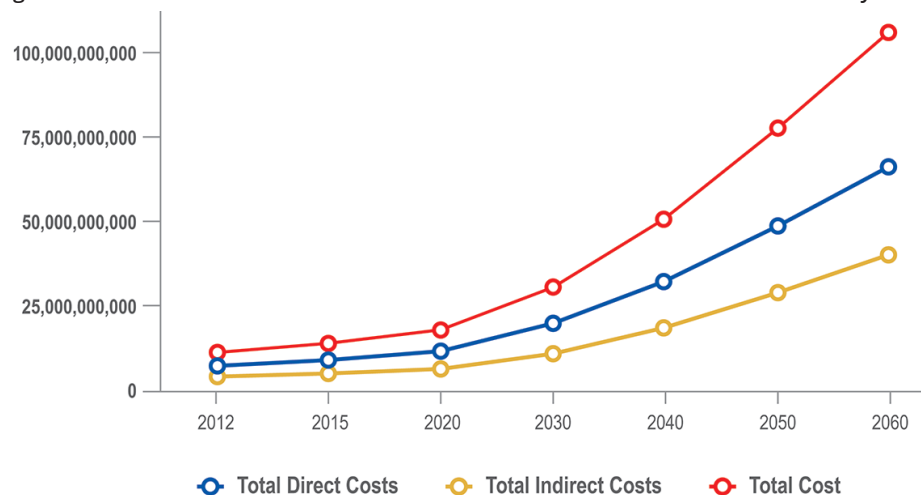
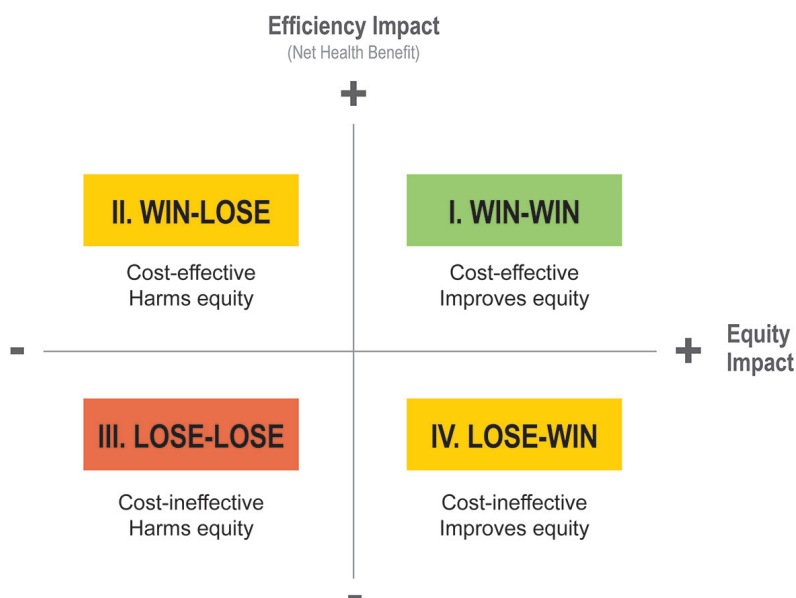


Figure 5: The efficiency-equity impact plane.



### Measuring Equity: Considerations for a Future Alzheimer's Therapy

Given the criticisms of the limited cost-per-QALY evaluations and the urgent need for greater brain health equity, what might a more equity-informed approach to a potential new Alzheimer's therapy look like?

In this case, value assessors would aim to maximize the total societal benefit of a treatment given its cost, or its “efficiency,” while also considering the treatment’s ability to reduce unfair inequality or its “equity.” Taking this approach, a new treatment’s benefits and drawbacks can be charted on an equity-efficiency impact plane. Such a plane can be divided into 4 quadrants, with efficiency impacts on the y-axis and equity impact on the x-axis.<sup>12</sup>

A new treatment’s potential value can then be divided into 4 categories—win-win, win-lose, lose-win, and lose-lose. In other

words, the treatment could: provide cost-effective benefits and improve equity (win-win); fail to provide cost-effective benefits but improve equity (lose-win); provide cost-effective benefits but reduce equity (win-lose); or fail to both provide cost-effective benefits and reduce equity (lose-lose) (Figure 5).

According to a recent analysis by the United Kingdom’s National Institute for Health and Care Excellence (NICE) of diverse therapies (not specific to Alzheimer’s disease), most new therapies fell into the win-win quadrant, with another large portion falling into the win-lose category.<sup>12</sup> Lose-lose and lose-win therapies were both uncommon.<sup>13</sup>

This framework provides several practical lessons for a potential Alzheimer’s therapy. First, a therapy should be considered most valuable if it both provides broad, cost-effective societal benefits and reduces inequity by addressing the disproportionate impact on women, racial and ethnic minorities, underserved communities, the elderly, and other groups. Second, through an equity lens, there is still value in a treatment that is relatively less cost-effective but reduces health inequity. Third, it is critical to develop strategies to ensure that a new treatment will reach those communities that need it most, in order to reduce inequity.

Finally, it should be noted that this “value-maximizing” approach is just one way of defining equity. Fairness can come in many different forms, and individuals and communities have diverse, varied conceptions of what fairness means. While

traditional value assessment focuses on maximizing value, there are 3 other important perspectives on equity: fair shares, moral rights, and fair processes.

Under a fair shares approach, resources are distributed in proportion to patients’ needs, offering each individual a fair chance at receiving needed resources. A rights-based approach assumes that patients have a fundamental right to benefits and care, no matter the cost. This involves concepts like the right to autonomy, the right to be treated with dignity, and the right to nondiscrimination. Fair processes of decision making focus on ensuring that decisions are made in a way that is impartial, accountable, inclusive, and transparent. These perspectives can broaden the discussion of value to include important, but hard-to-quantify concepts and priorities.

## Looking Ahead: New Tools to Advance Equity in Alzheimer's Disease

The equity concepts described above have growing real-world relevance in the Alzheimer's field, given the increasing likelihood of a new disease-modifying treatment. In fact, there already has been significant discussion and debate on this topic, and there is an ongoing discussion about how best to address the difficult moral questions of equity in future value decisions. New tools and models, including multicriteria decision analysis (MCDA) and value-based contracts, offer opportunities to incorporate equity considerations and better reflect the needs and priorities of those with lived experience of Alzheimer's disease.

As discussed above, QALY-based assessment, when leveraging QALYs alone, can have negative consequences for older, sicker members of society. These concerns were demonstrated in a 2005 decision from NICE that determined cholinesterase inhibitor drugs for the treatment of dementia were not cost-effective and should not be covered for UK's National Health Service patients.<sup>14</sup> NICE acknowledged the effectiveness of these drugs in the treatment of Alzheimer's disease, but it ruled that these benefits were not large enough to justify coverage. This decision led to significant controversy, as patient advocates argued that NICE was effectively discriminating against older, sicker people and ignoring the lived experience of those with the disease and their caregivers.

In the years since, there has been growing momentum for alternative tools that aim to address such challenges. One approach is MCDA, a comprehensive and holistic tool that can better incorporate aspects of equity and societal values.<sup>15</sup> MCDA is tailored to the decision-making process's particular objectives and conducted with the input of a range of stakeholders, including patients, clinicians, and ethics committees.<sup>16</sup> These stakeholders select the criteria that a given decision aims to achieve—giving a broader set of voices input into value decisions.<sup>16</sup>

Value-based contracts that consider patient preferences offer another way to address the challenges of traditional CEA.<sup>15</sup> Under these contracts, drug manufacturers and payers link coverage and reimbursement to effectiveness and utilization frequency; if a medication works and patients want to use it, utilization frequency will rise. Value-based contracts can also include reauthorization criteria that rely on a clinician's assessment of whether a patient is still receiving benefit.<sup>15</sup> These contracts reduce payer risk of suboptimal purchases, facilitate earlier access to therapies, and offer a more efficient pricing mechanism.<sup>15</sup> And, since utilization frequency is measured, value-based contracts can be a catalyst for enhanced real-world medical evidence.<sup>15</sup> These alternatives provide potential new directions to better integrate equity considerations and lived experience into future value decisions.

## Envisioning a Healthier, More Equal Society

New Alzheimer's disease therapies can move societies closer to brain health equity. This article offers 4 overarching conclusions:

- Alzheimer's disease generates disproportionate health and economic impacts on older adults, racial and ethnic minorities, and women, causing societies to fall short of brain health equity.
- QALYs alone do not account for these inequities or the value of treatments that could help to address them.
- Equity is an essential consideration for overall societal welfare, and it must be considered through multiple perspectives.
- Incorporating equity considerations into Alzheimer's value assessment and related deliberative processes requires evolving current processes and frameworks, potentially with MCDA and value-based contracts.

The next piece in this supplement will complement this article by examining evidence needs in long-term value demonstration.<sup>17</sup> We hope that these 3 pieces, taken together, will help evolve frameworks for value assessment in Alzheimer's disease, including recognizing equity as an essential consideration. •

Richard Cookson, DPhil, MPhil, professor at the Centre for Health Economics and co-director of the Equity in Health Policy Research Group, University of York, contributed to this manuscript.

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## Long-Term Value Demonstration in Alzheimer's Disease: Evidence Needs

Paola Barbarino, MA, Chief Executive Officer, Alzheimer's Disease International, London, England, UK; Anders Gustavsson, PhD, MSc, Partner, Quantify Research; Affiliate, Karolinska Institutet, Stockholm, Sweden; Peter J. Neumann, ScD, Center for the Evaluation of Value and Risk in Health, Tufts University School of Medicine, Boston, MA, USA



### The Need for Long-Term Value Demonstration in Alzheimer's Disease

There is a pressing need for payers, value assessors, and the broader Alzheimer's community to integrate real-world evidence into long-term value assessments. As discussed in the previous 2 sections of this supplement,<sup>1,2</sup> the burden of Alzheimer's escalates over the course of the disease and extends beyond direct medical costs, affecting caregivers, long-term care systems, economies, and society as a whole. However, current methods of evidence collection—such as clinical trials—do not account for these data elements, nor time horizons. Instead, they tend to focus narrowly on the outcomes that can be measured over a shorter period of time, thus leading to an important evidence gap when considering the longer-term impacts of early interventions.

As we look ahead at the disease-modifying therapies in the pipeline, we can anticipate that future innovative therapies can deliver value over a long period of time; and we can predict that a diversity of stakeholders will benefit from the treatments that delay cognitive, functional, and/or behavioral decline. Long-term value of new treatments must be better understood, and this need grows more urgent as disease-modifying therapies enter phase III trials.

This paper examines the need for long-term evidence as an essential part of Alzheimer's value assessments. It considers several key topics:

- The need for evidence to support greater access to Alzheimer's diagnostics earlier in the disease course, which is critical to maximize the value of a potential disease-modifying therapy
- Current gaps in real-world evidence, particularly the need for validated, early-stage outcome measures and the full range of long-term impacts, including for caregivers and healthcare systems
- Focus areas and potential solutions to facilitate long-term value demonstration
- Key actions to build a foundation for long-term value demonstration, as well as innovative payment models to balance affordability, access, and uncertainty

This paper aims to spur both discussion and research on long-term outcome measurement and value assessment in Alzheimer's disease. It rests on the foundational premise

that value assessments must adopt a broad perspective that considers a treatment's real-world benefits over time in order to measure the potential value of a novel Alzheimer's therapy.

### Evidence Needs for Early Detection and Diagnosis

Evidence needs in Alzheimer's disease start with detection and diagnosis. Access to screening, detection, and diagnosis is critical to effectively address the disease, yet current policies often do not support access to the necessary tests and tools because of a perceived lack of evidence of benefit. Greater evidence on the value of detection and diagnosis, including real-world data collected over an extended period of time, can help to make the case for access, laying the groundwork for earlier, more effective treatment with a potential disease-modifying therapy.

Long-term value of new treatments must be better understood, and this need grows more urgent as disease-modifying therapies enter phase III trials.

This is critically important, given the growing consensus that to detect and treat Alzheimer's disease in its earliest stages, health systems must have a strong emphasis on timely diagnosis. This would enable a disease-modifying treatment to have the greatest potential to alter or slow disease progression, maximizing the benefits for patients and potentially delaying care interventions. It should also reduce overall costs to health and care systems, families, and society.<sup>3</sup> Crucially, detecting Alzheimer's disease early allows families and people living with Alzheimer's disease to prepare adequately for what is to come. However, the benefits of this approach accrue over time and entail a broader set of outcomes than are currently measured. This creates the need for earlier, better real-world evidence for both diagnosis and treatment.

Figure 1 illustrates the potential benefits of this approach. As shown, an effective disease-modifying therapy would delay the decline in cognition and function, thereby giving patients more time in better health, reducing total costs and burdens by delaying the need for formal care, and potentially mitigating indirect costs like lost productivity and caregiver impacts.



Improving access to screening, detection, and diagnosis is the first step. Currently, it is estimated that at least half of patients with Alzheimer's disease and dementia are undiagnosed, and diagnosis, when it occurs, often happens 2 to 5 years after the onset of symptoms.<sup>4</sup> Therefore, diagnosis rates must be improved to maximize the benefits of a disease-modifying therapy.

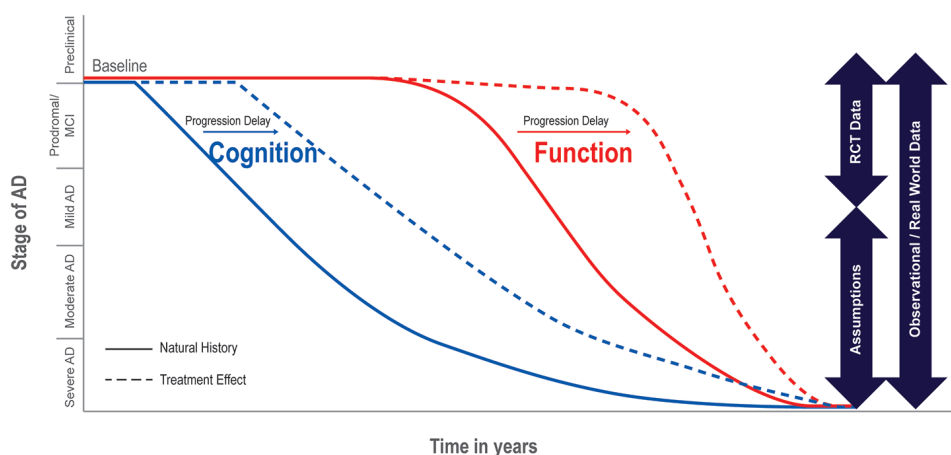
However, certain coverage recommendations and decisions for detection and diagnostics currently cite a need for more evidence of value. For example, in the United States, the US Preventive Services Task Force does not currently recommend cognitive impairment screening for older adults.<sup>3</sup> Further, the US Centers for Medicare and Medicaid Services has ruled that there is insufficient evidence to justify broad coverage of neuroimaging diagnostics like positron emission tomography (PET) and magnetic resonance imaging.<sup>5</sup>

## Gaps in evidence for diagnostics demonstrate the broader challenge of a lack of real-world data in Alzheimer's disease.

Real-world evidence can help to show the value of early detection, and if the evidence warrants it, to expand access to diagnostics, especially as disease-modifying therapies approach the market. For example, the Alzheimer's Association led the Imaging Dementia—Evidence for Amyloid Scanning (IDEAS) study to investigate the benefits of amyloid PET diagnostics with real-world evidence.<sup>5</sup> Enrolling over 18,000 Medicare beneficiaries, the IDEAS study found that amyloid PET led to changes in patient management in 60% of patients with mild cognitive impairment and 64% of patients with dementia of uncertain cause.<sup>6</sup> This imaging data resulted in a different diagnosis 36% of the time.<sup>6</sup> Furthermore, these benefits were found without a disease-modifying therapy available. If such a therapy were to become available, the potential real-world benefits of diagnosis would be even greater.

This work illustrates how real-world evidence can build the case for greater access to diagnosis. While it focuses specifically on PET testing, similar dynamics could apply to other procedures for early detection, such as cognitive screening, cerebrospinal fluid testing, or, eventually, blood-based biomarkers. Similar efforts will potentially be needed to examine the long-term, real-world benefits of other approaches to early detection and diagnosis.

**Figure 1: Long-term trajectory of people with Alzheimer's disease and the potential effect of a disease-modifying treatment.**



## Data Gaps: Assessing Needs in Real-World Evidence

Gaps in evidence for diagnostics demonstrate the broader challenge of a lack of real-world data in Alzheimer's disease. Currently, most data on Alzheimer's disease come from clinical trials that evaluate drug safety and efficacy with strictly controlled protocols for a set period of time.<sup>7</sup> This approach is unlikely to capture the full benefits of a disease-modifying therapy, which may include more outcomes and a longer period of time than measured in clinical trials.

For example, in the United Kingdom, the National Institute for Health and Care Excellence's guidelines state that the "time horizon for estimating clinical and cost-effectiveness should be *sufficiently long* [emphasis added] to reflect all important differences in costs or outcomes between the technologies being compared."<sup>8</sup> A lifetime perspective is appropriate in most cases and data should be extrapolated beyond the duration of a clinical trial.<sup>9</sup>

But what outcomes should be measured directly versus extrapolated, in which populations, and for how long?

To answer these questions, the European ROADMAP project (Real-World Outcomes Across the Alzheimer's Disease Spectrum: A Multimodal Data Access Platform) "aim[ed] to deliver a series of methods and tools that will allow the scalable, transferable integration of data on patient outcomes in the real world."<sup>10</sup> As a starting point, ROADMAP assessed current data sources and identified existing gaps in real-world evidence.

This approach is illustrated in Figure 2, which shows the ROADMAP project's "data cube."<sup>7</sup> The cube's 3 axes represent data sources, disease stages, and outcomes, showing where additional research is needed. Although ROADMAP assessed diverse sets of data, including population-based databases, national registries, electronic health records, disease registries,

and randomized controlled trial data, the cube makes clear that no data source is comprehensive. Even valuable sources are limited in the outcomes and data sources they measure. As a visual representation of these limits, the cube aids researchers in targeting gaps early, enabling them to be filled in advance of any therapy's review by a regulatory or value assessment body.

ROADMAP has identified 2 of the most pressing real-world evidence needs: (1) validated outcome measures for the earliest asymptomatic stages of Alzheimer's disease; and (2) real-world evidence that shows a therapy's long-term effects across numerous stages of disease, including on outcomes, caregivers, and healthcare systems.<sup>7</sup>

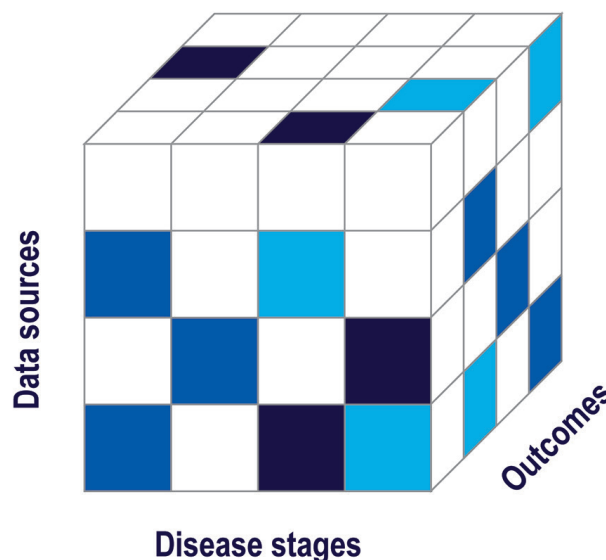
First, validated and well-established outcome measures are necessary in early symptomatic stages of Alzheimer's disease (including prodromal Alzheimer's), as new treatments will likely target these stages of the disease for the first time. Since a treatment that is effective in these stages will need to prevent or delay clinical symptoms, the research community must build consensus on what constitutes a meaningful delay in disease progression. However, information about early clinical symptoms of Alzheimer's is limited, impeding accurate measurement of the early effects of the disease.<sup>7</sup> To fill this evidence gap, the research community can identify effective and reliable instruments to measure cognition as subtle symptoms start to emerge. These instruments must be applicable in real-world environments like the home—not just in strictly controlled clinical trials.

**From the patient perspective, there is a lack of granularity in the knowledge about the different patient subgroups and disease substages, especially in the early stages of the disease.**

Although there are many validated screening tools used to detect mild cognitive impairment (MCI), most are only validated in the memory clinic setting, rather than in the general population.<sup>11</sup> There are currently 80 pen-and-paper tests for MCI that have been validated in memory clinic settings, and there exist validation studies for 7 computer-based MCI screening tests.<sup>11</sup> However, only 2 pen-and-pencil tests for MCI detection have been validated in a population-based cohort, and only 1 computer-based test has been validated in a population-based cohort.<sup>11</sup> Although these tests reflect meaningful outcomes to patients, a lack of validated real-world data is a barrier to consensus on how to interpret clinically meaningful cognitive changes.

Second, real-world evidence is needed to assess a therapy's long-term impacts across a broader set of outcomes than those typically used in clinical trials to support product registration, including outcomes of importance for caregivers and healthcare systems. As discussed in the first paper of this supplement by

**Figure 2: The ROADMAP Data Cube visualizes the project's 3 key activities and how they contributed to identify key gaps across Alzheimer's disease stages, outcomes, and data sources. Colors indicate the relative availability of relevant data. Darker colors show where more relevant data exist, while lighter colors indicate where data needs are greater.**



Garrison et al,<sup>1</sup> these benefits constitute a significant share of potential value in Alzheimer's disease.

In particular, ROADMAP proposed a framework for using real-world evidence to assess caregiver impacts.<sup>7</sup> The framework holds that caregiver-relevant outcomes should be established by consensus. These outcomes may include quality of life, health status, loss of income, and caregiver time; all of which are key factors in health economics modeling. Overall, ROADMAP called for international consensus on which outcomes will inform regulatory and health technology assessment decisions. With consensus, international coordination is needed to actually generate the real-world evidence on these outcomes. Importantly, pharmacoeconomic analysis needs data that will enable it to consider distinctions between national and regional settings, such as differences in relevant outcomes, costs, and unique care delivery characteristics.

By filling these real-world evidence gaps, stakeholders can provide a more accurate analysis of the true costs of Alzheimer's disease across an entire society. This would establish the basis for value assessment that more fully captures the disease's immense costs and the potential value of treatment advances.

### **Potential Solutions: Identifying Focus Areas for Long-Term Value Demonstration**

To address these gaps, progress is needed on 2 fronts: (1) data collection; and (2) leveraging the data in value assessments.

#### **Data Collection**

In the area of data collection, there is a critical need for more evidence on financial impacts and total costs. Real-world

evidence is often used to assess whether results from a clinical trial carry over into the real world. But it can also be used to address one of the most important gaps in current Alzheimer's value assessment: the overwhelming financial strain on families, communities, the workforce, and health systems. These costs extend far beyond the direct expenses of medical treatment and care, but the potential value of reducing these real-world impacts is neither measured by clinical trials nor fully captured by existing value assessment frameworks.

## Building the consensus, infrastructure, and evidence base for long-term value demonstration in Alzheimer's disease will require concerted efforts and collaboration between many different stakeholders over the course of multiple years.

To better evaluate a new disease-modifying therapy's effects on the total costs of Alzheimer's disease, real-world evidence should expand the scope of cost-effectiveness evaluations beyond the healthcare payer perspective. The financial cost of Alzheimer's disease is distributed throughout society, with patients and caregivers bearing the brunt of the economic burden. In 2016, the estimated global costs of Alzheimer's disease and dementia were \$948 billion, and costs are projected to increase 15.94% each year as disease prevalence and care expenses rise.<sup>12,13</sup> Critically, direct medical costs—those covered by healthcare payers—account for just 16% of total costs, while social care costs account for 42.3%, and informal care and indirect costs account for 41.7%.<sup>14</sup>

A new disease-modifying therapy in Alzheimer's disease can potentially lower not just direct medical costs, but the much larger downstream nonmedical, indirect, and spillover costs. These savings compound over time and fall outside the balance sheet of healthcare payers.

Real-world evidence can help correct these evaluations, but there are challenges. Overall, there is a high degree of heterogeneity in the Alzheimer's disease community. From the patient perspective, there is a lack of granularity in the knowledge about the different patient subgroups and disease substages, especially in the early stages of the disease. From the provider perspective, there is a lack of consensus on the right outcomes to include in real-world evidence collection. Further, data and biomarkers are rarely digitalized nor harmonized between different systems, and there are often technical and legal barriers to data infrastructures.

Initiatives are attempting to solve these challenges. For example, the US National Alzheimer's Coordinating Center (NACC) offers rich data on thousands of patients that can be accessed by researchers all over the world.<sup>15</sup> The Swedish dementia register (Svedem), another example, has complete national coverage of

specialist care and approximately 75% of primary care centers, collecting longitudinal clinical data on some 90,000 dementia patients to-date.<sup>16,17</sup> These data sources have been and can be used to develop models for assessing the long-term benefits of new candidate treatments.<sup>17,18</sup>

However, there is still room for improvement, particularly in 3 interlinked areas: the Alzheimer's model, outcomes, and data. First, the model representation of Alzheimer's disease can be improved. As noted above, it should be comprehensive enough to encompass the impact on all stakeholders, and therefore have a societal and long-term perspective. It should also be granular enough to represent the continuous and slowly progressive disease which is Alzheimer's. Today, we have a rather granular representation of the dementia stage, whereas the predementia stage is often crudely represented as an annual conversion from MCI to dementia. Finally, we can better acknowledge the heterogeneity of the Alzheimer's population, by considering the impact on different subgroups (eg, as defined by age or genetic profiles) and making sure all cohorts under evaluation are well defined with stringent eligibility criteria.

Second, outcomes are particularly difficult to assess in Alzheimer's disease because there are no clear, clinically meaningful events, such as a fracture or stroke in other diseases. Instead, complex measurements of pathology biomarkers and clinical symptoms are collected within trials, but with limited meaningfulness to patients.<sup>19</sup> Real-world data can help describe how these intermediate outcomes are connected to the longer-term outcomes of value to patients, caregivers, and society as a whole. Also, digitalization of the measurement of clinical symptoms may improve their accuracy and efficiency in both clinical practice and research.<sup>20,21</sup>

Third, data have inherent challenges that have the potential to be solved by effort and collaboration. An effective infrastructure is needed to compile the large and longitudinal databases that are required to describe this disease. There are technical and legal barriers, which stem from the sensitive nature of health data. These challenges can be overcome by engaging all stakeholders, including policy makers and patient organizations, conveying a joint message that these data are essential for improving public health.

Collaboration is also needed to harmonize the data, such as establishing uniform data and core outcomes sets. This would enable comparison and pooling of multiple data sources. Some types of data will not be representative across settings and country borders, which re-emphasizes the need for well-defined study populations.

Finally, validation efforts should be made to compare and explain remaining differences across different data sources. As an example, the International Pharmaco-Economic Collaboration on Alzheimer's Disease (IPECAD), held a workshop in September 2020 where a dozen developers ran their Alzheimer's models

based on a variety of the available real-world data sources, but with a jointly agreed treatment scenario. The inputs and outcomes were compared and scrutinized in an attempt to systematically explain differences across models, and to learn from this process (see IPECAD.org).

### ***Integrating Data Into Value Assessment***

At the same time as data collection improves, value assessors can capture the costs of Alzheimer's across society during a longer time span. Cost-effectiveness frameworks can reflect the many stakeholders who benefit from new treatments. Frameworks can include outcomes like quality of life, needs for full-time care, levels of dependency, and the onset of advanced disease states.

Furthermore, value assessors can use sensitivity analyses to test alternative discounting frameworks. Discounting calculates the current value of financial benefits that will be gained in the future, enabling measurement of changing therapy benefits over time. However, current discounting methods, which follow country-specific guidelines, struggle to make accurate assumptions about the magnitude and timing of drug effects.<sup>22</sup> As a result, they can overvalue short-term benefits and undervalue medium- and long-term benefits.<sup>22</sup> As the greatest financial benefits of a new disease-modifying therapy will come in the medium- to long-term, alternative discounting methods are needed to accurately value new Alzheimer's drugs.<sup>22</sup>

Building the consensus, infrastructure, and evidence base for long-term value demonstration in Alzheimer's disease will require concerted efforts and collaboration between many different stakeholders over the course of multiple years. It is important to accelerate progress in this area in order for real-world evidence to inform value decisions.

### **Next Steps: Building a Foundation of Long-Term Value Demonstration and the Potential Role of Innovative Payment Models**

Progress is needed on 2 fronts: (1) creating the foundation for long-term value demonstration; and (2) exploring the role of innovative assessment and payment models.

In the near-term, stakeholders can use models to identify key drivers of long-term value, especially by starting models earlier in a patient's life course and modeling real-world scenarios, considering factors like diagnosis, subgroups, and adherence. Stakeholders must also start to fill data gaps, like those mentioned above, as well as costs and utilities by stage, comorbidities, caregiver utilities, and societal impacts. Stakeholders can also validate biomarkers and consider health and societal perspectives.

However, while a larger base of real-world evidence is essential, it will not solve all Alzheimer's value and payment challenges, especially if a new therapy is approved before these efforts

are completed. Therefore, there is also a need for innovative payment models, which can balance access, the potentially high cost of a new treatment, and the uncertainty of long-term outcomes. Two potential approaches are outcomes-based payment models and subscription agreements. Outcomes-based payment models leverage real-world evidence to substantiate value, which affects price and access. Subscription models are agnostic of product performance and leverage innovative payment cycles.

**To further facilitate drug access, governments must ensure positive long-term incentives for investing in drug development.**

Within outcomes-based payment models, a performance-warranty approach compensates drug manufacturers based on patient outcomes obtained with real-world use of the product.<sup>3</sup> If a treatment is observed to be effective based on predetermined criteria, the manufacturer receives full compensation. If it does not reach efficacy requirements, the manufacturer receives only partial compensation. This approach distributes risk between manufacturers and payers, while providing access to patients. In effect, it reduces uncertainty in the treatment outcomes by "building in" real-world evidence for payment.

Costs can also be distributed with subscription payment models. In this approach, a health system pays manufacturers a fixed amount for drug access, regardless of the number of patients served.<sup>3</sup> This arrangement allows for cost management as patient populations increase, while offering a reliable revenue stream for manufacturers.

As one example, the subscription model has been successfully applied to hepatitis C. When hepatitis C therapies were introduced in 2015, they cost \$100,000 per patient.<sup>3</sup> To manage costs while serving a large patient population, the states of Washington and Louisiana negotiated subscription agreements. These arrangements offer a model that can be adapted to Alzheimer's disease because they benefit payers, patients, and drug manufacturers alike.

To further facilitate drug access, governments must ensure positive long-term incentives for investing in drug development. At the same time, drug manufacturers must clearly demonstrate a therapy's value with sound empirical evidence.<sup>3</sup> Innovative payment models can help to balance these 2 imperatives, while ensuring that evidence barriers do not impede access for patients.

### **Preparing for the Future of Long-Term Alzheimer's Value Assessment**

Although long-term evidence needs in Alzheimer's are vast and will certainly evolve as research progresses, leading scholars point to several key conclusions:

- A safe and effective disease-modifying Alzheimer's treatment will likely deliver value over the course of many years and many different stakeholders, creating a need for long-term value demonstration.
- Real-world evidence on diagnostics can help to enable widespread early detection, which is critical to maximize the benefits of disease-modifying treatment.
- Gaps in real-world evidence impede long-term measurement of disease cost to society and potential value.
- Greater collaboration is needed to facilitate real-world evidence and long-term value demonstration, including consensus on outcomes, data, and modeling.

- Innovative payment models can help to ensure a therapy's affordability and access.

We urge further research to develop real-world evidence initiatives and innovative value frameworks that can accurately, holistically, and equitably assess the value of future therapies in Alzheimer's disease. •

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