MAY/JUNE 2025 VOL. 11, NO. 3

VALUE & OUTCOMES SPOTLIGHT

A magazine for the global HEOR community.

TIED TO THE PAST, UNPREPARED FOR THE FUTURE: MEETING THE ALZHEIMER'S DISEASE CHALLENGE WITH HEOR

ISPOR
Improving healthcare decisions

VALUE & OUTCOMES SPOTLIGHT

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A magazine for the global HEOR community.

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.

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Advancing Alzheimer's Disease Research Through Health Outcomes and Real-World Evidence

Alzheimer's disease (AD), a progressive neurodegenerative condition, is increasingly recognized as one of the paramount global health challenges. Affecting over 55 million people worldwide, with projections estimating 152 million cases by 2050, AD demands urgent attention not merely for its medical implications but for the extensive societal ripple effects it provokes. As the incidence of AD rises unabated, the conundrum of how best to integrate health outcomes research with real-world evidence (RWE) emerges as a critical frontier in the ongoing quest to mitigate the impact of this formidable disease.

Central to this discourse is the intrinsic value of health economics and outcomes research in elucidating the economic undulations wrought by AD. Annually, dementia costs surpass $1.3 trillion globally, encompassing medical treatments, nursing home care, and informal caregiving provided at significant personal sacrifice. This financial burden is exacerbated by the silent epidemic of undiagnosed cases, particularly in low- and middle-income countries, where stigma and limited healthcare resources hinder timely diagnosis and access to support systems. It is estimated that only 25% of dementia cases are correctly diagnosed, leaving millions without adequate care and grooming systemic inequities across health landscapes.

> Alzheimer's disease demands urgent attention not merely for its medical implications but for the extensive societal ripple effects it provokes.

The growing pipeline of over 100 potential AD treatments in advanced clinical trials offers hope. The latest therapeutic advancements, marked by the advent of monoclonal antibodies such as lecanemab and donanemab, offer promise by potentially altering the disease trajectory. These drugs aim to decelerate cognitive deterioration by targeting and ameliorating amyloid plaques—a hallmark of AD pathology. Yet, while promising, their efficacy, accessibility, and economic viability remain points of contention among healthcare professionals and policy makers. Concerns about their cost-effectiveness juxtapose the financial promise they hold in potentially reducing the overall societal costs of managing AD.

RWE is instrumental in bridging gaps between clinical trial data and actual patient outcomes. Unlike controlled clinical environments, RWE reflects the nuanced impacts of Alzheimer's treatments in diverse healthcare settings, capturing variations in disease progression and response to interventions. Such evidence is vital for informed policy decisions and for optimizing the allocation of healthcare resources. Models like the GUIDE program, which aims to streamline dementia care in the community, emphasize the utility of RWE in driving policies that enhance quality of life for patients, and alleviate the burdens on caregivers.

The engagement of caregivers—often the unsung heroes in navigating AD—is crucial in this ecosystem. Caregivers shoulder immense emotional and financial burdens, often at the expense of their personal and professional lives. They render invaluable services through unpaid care, illuminating the urgent need for systemic reforms that integrate caregiver support into health policy frameworks. Technological interventions—such as virtual reality tools for early detection—promise to bolster these support systems, easing caregiver burdens and improving outcomes for patients.

Despite these burgeoning innovations, significant gaps remain in the care ecosystem. In the United States, 20 states are classified as "dementia neurology deserts" due to shortages of geriatric specialists and diagnostic facilities. Globally, up to 90% of dementia

cases in low-income countries go undiagnosed, reflecting disparities in access to care. Addressing these challenges requires coordinated efforts to expand diagnostic capacity, improve care coordination, and support caregivers. Innovative models, such as Japan's Orange Plan and South Korea's "war on dementia," demonstrate how government-led strategies can drive systemic change.

AD research faces precarious crossroads. Funding fluctuations and budget cuts threaten to stall research progress at a pivotal moment. The National Institutes of Health envisages a stark shortfall in meeting the mandates of the National Plan to Address Alzheimer's Disease, jeopardizing the momentum of breakthroughs critically needed to curb this escalating crisis. Moreover, proposed reductions in diversity, equity, and inclusion research funding could severely impact women's health studies—a vital consideration given that women comprise nearly two-thirds of the AD patient demographic.

> Alzheimer's disease poses a multifaceted threat exacerbated by societal and economic factors, demanding a concerted global response.

AD poses a multifaceted threat exacerbated by societal and economic factors, demanding a concerted global response. Advancements in therapy, ongoing research initiatives, and a robust integration of RWE into health policies constitute promising avenues toward addressing AD more effectively. Ensuring equitable access to care, empowering caregivers, and steadfastly pursuing research funding are imperative as nations strive to accommodate the mounting demands of an aging global population. As we stand at the cusp of transformative breakthroughs, the collective commitment to harnessing RWE offers hope for a more balanced and sustainable approach to battling AD. The time to act is now—AD demands urgent attention, innovation, and systemic change.

As always, I welcome input from our readers. Please feel free to email me at zeba.m.khan@hotmail.com.

Zeba M. Khan, RPh, PhD
Editor-in-Chief,
Value & Outcomes Spotlight

FROM THE CEO

Hope in the Dark: HEOR's Value in Alzheimer's Disease Research and Treatment

Rob Abbott, CEO & Executive Director, ISPOR

To suggest that Alzheimer's disease (AD) is an insidious affliction is to perfect the art of understatement; it erodes—and ultimately destroys—patients' memories and robs family and friends of loved ones long before death. Nearly 3 decades on, I still get chills thinking of the day my father no longer recognized his wife of nearly 50 years. Such is the emotional and psychic impact of AD. It is also a truly global health issue—the seventh leading cause of death worldwide—with nearly 90 million people living with "early AD" and at least another 30 million coping with mild, moderate, or severe forms of the disease. Worse, the global prevalence of dementia, of which AD accounts for 60% to 80%, is predicted to triple by 2050 due largely to an aging population. In the United States, 1 in 9 Americans aged 65 and older has AD and by 2030, 20% of the US population is expected to be age 65 years or older, so the number of Americans suffering from this fatal form of dementia could increase significantly.

> One of the most challenging–and frightening–aspects of AD is that symptoms can begin having an impact on people well before a formal diagnosis is ever made. In some cases, decades before.

Against this backdrop, I welcome the editorial focus of *Value and Outcomes Spotlight* on health economics and outcomes research (HEOR) and its contribution to research and treatment of AD. I'm especially interested in the contributions the papers in this issue make regarding the demonstration of value in AD research and treatment. This, of course, means that the patient and caregiver perspective is vital in helping to grow our collective understanding of how patients and their caregivers think about value.

AD is characterized by the accumulation of toxic amyloid-beta plaques, tau tangles and neuroinflammation in the brain, which causes irreversible neuronal loss and a progressive decline in cognitive function. Ultimately, AD interferes with a person's ability to perform everyday tasks unassisted. In late-stage AD, it is not uncommon for a patient to become confused, unable to communicate, and completely dependent on others for care.

One of the most challenging—and frightening—aspects of AD is that symptoms can begin having an impact on people well before a formal diagnosis is ever made. In some cases, decades before. The most common expression of this might be memory loss, which can be incorrectly attributed to normal aging. Sadly, by the time many people with AD see a physician, they already have mild cognitive impairment. For those people unfortunate enough to be diagnosed with mild cognitive impairment due to AD, progression to dementia is inevitable.[i]

Historically, treatment protocols for AD were modest; symptomatic treatments with temporary benefits were the norm, and there was no material impact on long-term health outcomes. More recently, scientific progress has seen the onset of disease-modifying treatments that target AD progression. The accelerated approval of lecanemab by the US Food and Drug Administration is an example[ii]—this anti-amyloid immunotherapy has been shown to slow cognitive decline in people with mild cognitive impairment and mild AD-related dementia. This, in turn, creates the potential for people with AD to enjoy a higher quality of life for longer, and equally, to relieve some of the burden from care partners and the healthcare system more broadly.

I would be remiss if I didn't mention ISPOR's deep interest and activity in advancing the science of AD research and treatment. Earlier this year, *Value in Health*, the official journal of the Society, published a special themed section of research papers that offer crucial insights into the complex health economics of AD and related dementias. Collectively, the papers offer a roadmap for future research, policy development, and treatment as the global population ages and novel treatments emerge.

> As the CEO of ISPOR, one of the things–maybe even the thing–that excites me most is the opportunity to champion research and the translation of that research into HEOR insights that shapes new and better policy decisions.

This issue of *Value & Outcomes Spotlight* is a beautiful complement to the works published earlier in *Value in Health*. They help us continue the journey to understanding both the trajectory and time horizon for AD as well as the economic implications of the disease—this is particularly important given that the health impacts and costs can be spread over decades. At the same time, the challenges of AD open up new vistas of possibility from a research and methods development perspective. How might we, as ISPOR, think differently about the definition of value in the context of a chronic disease like AD? What new methods might we, as the professional society for HEOR, advance to improve on cost-effectiveness measurement

for AD? These are just some of the questions that lie beneath the surface.

As the CEO of ISPOR, one of the things—maybe even the thing—that excites me most is the opportunity to champion research and the translation of that research into HEOR insights that shapes new and better policy decisions. This, in turn, should lead to better outcomes for patients. In the case of diseases like AD there are so many opportunities for ISPOR to make a difference: standardizing economic evaluation methods, articulating more rigorous approaches to the measurement of economic impact(s), and ensuring equity in access to new treatments, to name a few. There are also imperatives to consider how we might use artificial intelligence algorithms to accelerate diagnosis and treatment. The focus on this topic by both *Value in Health* and *Value & Outcomes Spotlight* galvanize my resolve to keep pushing forward and catalyze my thinking about where and how to push for maximum effect. The journey is really just beginning but there are signs of progress and clues to where we should place our feet next. All that is needed is the will to keep going. On behalf of patients with AD and their families and caregivers, and healthcare systems globally, I pledge to keep going.

[i] And the impact of AD is not limited to the patient; the burden of care on partners and other family members is considerable—and greater than for most other chronic diseases. It is clear, for instance, that work productivity, emotional health, and the overall quality of life of care partners and family members of people with AD are compromised relative to the rest of the population.

[ii] FDA approval in 2021 of aducanumab, a therapy targeting the fundamental pathophysiology of AD, is another, although not without controversy given its treatment cost.

Creating a Collaborative Community in HEOR

The ISPOR 2025 annual conference was held in Montreal from May 13-16, 2025. The conference theme, "Collaborating to Improve Healthcare Decision Making for All: Expanding HEOR Horizons," highlighted how health economics and outcomes research can empower data-driven, patient-centered decision making that leads to more equitable, accessible, and effective healthcare for all.

Photos from the event capture the collegiality and collaboration that reflects the essence of the ISPOR and HEOR community. For more news and photos from the conference, visit ISPOR's HEOR News Desk.


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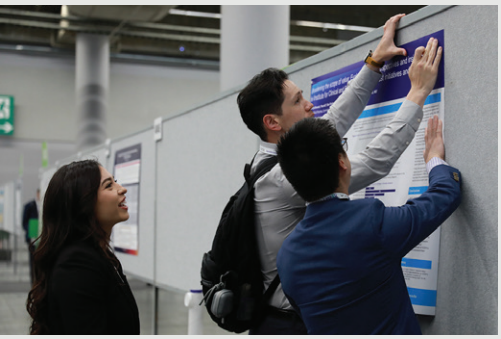


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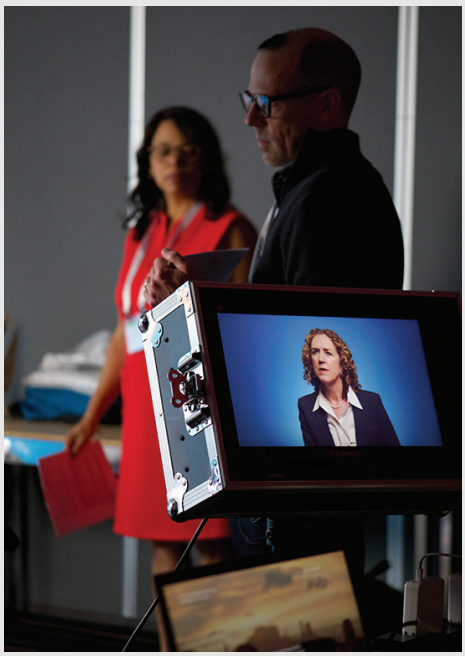


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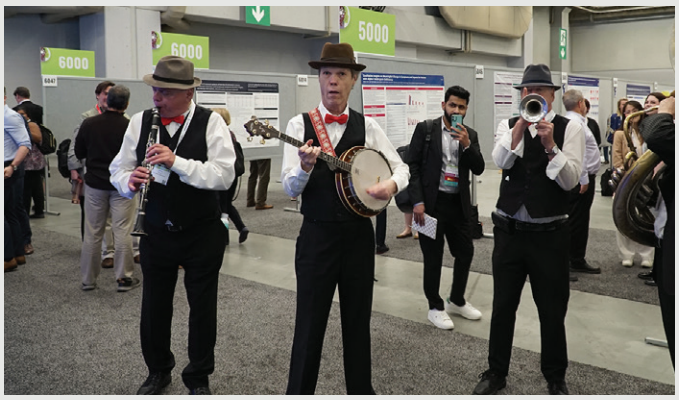
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HEOR NEWS

1 Health Technology Assessment: First Joint Clinical Assessments Begin (EU Health and Food Safety Directorate General)

The first 2 joint clinical assessments for medicinal products have started under the Health Technology Assessment Regulation (EU 2021/2282)—the studies are for a pediatric cancer treatment and an advanced therapy medicinal product to treat skin cancer. Read more

2 White Paper on Advancing Environmental Sustainability Through Health Technology Assessment (International Network of Agencies for Health Technology Assessment)

The paper aims to advance the discussion of the potential readiness and role for health technology assessment agencies to integrate environmental impact assessment into their evaluations, and to inspire these groups to work together to reduce the environmental footprint of healthcare and support health systems to deliver high-quality, cost-effective, and environmentally sustainable care. Read more

3 Top 10 Research Priorities in Global Burns Care: Findings From the James Lind Alliance Global Burns Research Priority Setting Partnership (The Lancet Global Health)

Researchers say the main strength of this priority-setting partnership is the breadth of its international engagement and multisource data collection, believing it is the most international such James Lind Alliance exercise to date, and it could provide valuable lessons for future prioritization work in other fields. Read more

4 Estimated Undertreatment of Carbapenem-resistant Gram-negative Bacterial Infections in 8 Low-income and Middle-income Countries: A Modeling Study (The Lancet Infectious Diseases)

In looking at 8 selected countries, researchers estimated that Infections caused by CRGN bacteria are likely to be significantly undertreated in LMICs and recommend improved access to diagnostics and antibiotics, strengthening of health systems, and research to identify gaps in the treatment pathway are needed. Read more

5 Healthcare-associated Infections, a Threat to Residents of Long-term Care Facilities in Europe (European Centre for Disease Prevention and Control)

A new ECDC survey reveals that 3.1% of the residents in long-term care facilities had at least one healthcare-associated infection at the time of the study, pointing to serious gaps in infection prevention and control measures, as well as antimicrobial stewardship in elder care facilities. Read more

6 Medical Journals Coming Under Scrutiny From Trump Administration (Harvard T.H. Chan School of Public Health)

After 2 medical journals received letters from a top US attorney asking for responses to questions about alleged bias, scientists are expressing concern about potential Trump administration interference in the journals' work. Read more

7 Robert F. Kennedy Jr Asks Centers for Disease Control and Prevention for New Measles Treatment Guidance Amid His Unfounded Claims (CBS News)

Health and Human Services Secretary Robert F. Kennedy Jr. will ask the CDC to develop new guidance for treating measles with drugs and vitamins, an HHS spokesperson said. Read more

8 Trump Administration Slashes Research Into LGBTQ Health (New York Times)

The Times found that more than $800 million in grants cancelled through early May addressed the health of sexual and gender minority groups, including studies of cancers and viruses that tend to affect members of these groups, and the cancellations will set back efforts to defeat a resurgence of sexually transmitted infections. Read more

9 Scientists Question National Institutes of Health Project's Use of 20th Century Technology to Make a Universal Flu Vaccine (STAT)

As the Department of Health and Human Services announced that it was investing half a billion dollars on an NIH project to develop a vaccine platform for pathogens that could trigger pandemics, scientists are puzzled as to why the project is using the whole killed viruses method pioneered in the 20th century and overtaken by newer, more nimble production processes. Read more

10 Canada's Drug Agency Announces New 5-year Strategic Plan (Canada's Drug Agency)

The first strategic plan for the agency aims to power evidence-driven drug, health technology, and health system decisions supported by guiding principles of excellence, agility, partnership, inclusion, diversity, equity, accessibility, and integrity. Read more

Impact of Delayed Patient Access to Cancer Treatment

Marco Gross-Langenhoff, PhD, Astellas Pharma, Munich, Germany; **Mathias Flume, PhD, MBA**, KVWL, Dortmund, Germany; **Shilpi Swami, MSc**, ConnectHEOR, London, United Kingdom; **Jörg Ruof, MD, PhD, MBA**, European Access Academy, Basel, Switzerland

Introduction: The Evolving Oncology Space

Cancer remains one of the leading causes of death worldwide, responsible for nearly 10 million deaths in 2020.[1] Nearly half of all individuals will be diagnosed with the disease at some point in their lives,[2] making continued research and innovation critical. To support and incentivize these efforts, various initiatives and frameworks have been established, for example Cancer Moonshot in the United States, Europe's Beating Cancer Plan, or the World Health Organization's Controlling Cancer.[2-5] Developments over the last decades led to significant improvements in 5-year survival rates, particularly in regions like the United States.[6]

The evolution of cancer treatment has been marked by major breakthroughs over the past century (**Figure 1**).[7] In the early 1900s, surgery and radiotherapy were the primary methods for combating the disease. Since the mid-20th century, chemotherapy was a mainstay of cancer treatment. Scientific advancements in fields such as genomics, transcriptomics, and proteomics enabled a surge in new modalities since the 1990s, such as targeted therapies, be it small molecule kinase inhibitors and monoclonal antibodies. The 2010s introduced immune checkpoint inhibitors, which revolutionized cancer treatment and lay the groundwork for more recent innovations including CAR-T cell therapy, antibody-drug conjugates, bispecific antibodies, and radioligand therapy, all of which have transformed oncology by providing more precise and effective treatment options.[7]

Despite these advancements, ensuring patient access to new treatments remains a significant challenge. Research activity in oncology is at an all-time high,[8] and the number of approved cancer medications by regulatory bodies such as the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) has profoundly increased since 2000.[9,10] However, the availability of these treatments varies across different regions, as will be discussed further, with considerable delays.[11,12] Understanding the reasons behind these delays and their implications is crucial for developing solutions for improving patient access to modern oncology treatments. This requires coordinated efforts, as it will be discussed from different perspectives in the following.

A Payer Perspective

To highlight a payer's perspective, there are multiple challenges in ensuring timely patient access to novel oncology treatments.

Recent data comparing access timelines across 6 European countries underscore the significant variability in the time from EMA approval to actual patient access, both between and within countries. This delay persists even after national reimbursement decisions, revealing systemic inefficiencies beyond regulatory approval.[13]

The payer perspective is not monolithic, but rather spans 3 key dimensions:

- Individual patient perspective: Timely access is critical in oncology, where delays can directly impact survival, especially in advanced disease stages. Despite EMA or national reimbursement, patients often face further delays at the hospital/specialist level.
- Drug portfolio management perspective: Payers must assess whether a new treatment provides added therapeutic value over the current standard of care. The availability of robust clinical data and a sound health technology assessment (HTA) analysis on additional benefits often lags significantly behind regulatory approval. Distinctions between true innovations and "me-too" products are essential for informed decision making and pricing.
- Population and system perspective: Health systems must balance early access with financial sustainability. Granting access at high initial prices can weaken a payer's negotiating position. Moreover, not all negative reimbursement decisions are budget-driven—some reflect limited evidence on additional benefit versus standard of care.

There is no single solution to these access challenges from a payer's perspective. Payers are committed to delivering effective treatments but must navigate a complex interplay of budget constraints, HTAs, and pricing dynamics (**Figure 2**).

The upcoming European Joint HTA framework may support more consistent and evidence-driven access decisions, ultimately benefiting both patients and healthcare systems.

A Health Economist Perspective

Delays in access to oncology treatments carry profound health and economic consequences. A health economist's perspective is critical in identifying, quantifying, and addressing these wider impacts to ensure decisions are not only clinically sound but economically sustainable.

Figure 1. The evolution of cancer therapy

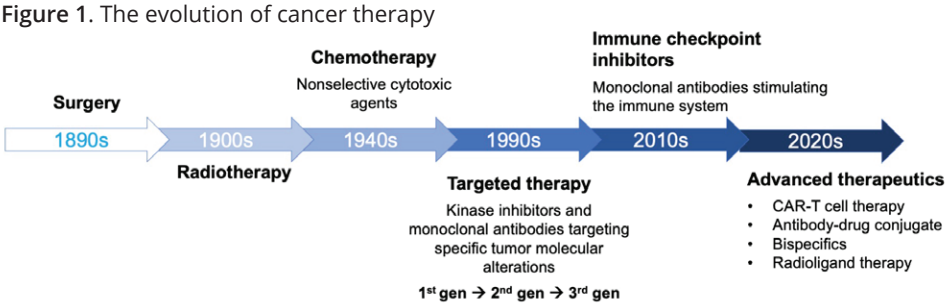
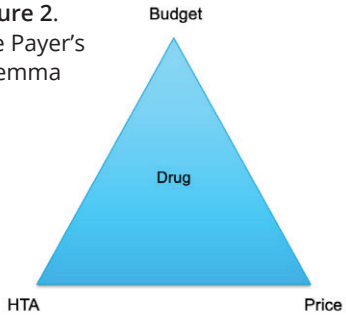


Figure 2. The Payer's Dilemma



Delays aren't just regulatory hurdles; they have measurable human and economic consequences, and they present challenges in multiple layers:

- Patient challenges: Heavy out-of-pocket treatment expenditure, indirect costs, and outcomes such as early progression, shorter survival, and low quality of life
- Societal impact: Caregiver burden, productivity loss, and equity considerations
- Payer dilemma: Budget constraints, HTA processes, population health maximization, and pricing negotiations
- Industry perspective: Pricing and reimbursement strategies, financial uncertainty, and slowdown in investment in research and development

The health economist considers multiple perspectives, ranging from clinical to economic to policy-driven, and synthesizes them into actionable insights for decision making. The key impact categories to measure the full impact of delays include direct costs, indirect costs, health outcomes, healthcare system costs, and wider impact on society (**Figure 3**).

Although there are a limited number of studies, the existing evidence confirms these modeled assumptions with global real-world data[14]:

- Globally, an incremental societal value ranging from $38,000 to more than $1 million per newly treated patient per month, due to early reimbursement.[15]
- For each year of drug approval acceleration, a median of 79,920 life-years per drug could be saved worldwide.[16]
- The societal value of life-days lost per patient ranged from $32,148 in Italy to $101,565 in Australia.[17]
- Across various countries, delayed access to oncology drugs potentially resulted in the loss of more than 30,000 life years. Total potential progression-free life years lost were 48,037 in Canada. The worst delays (~15 years) resulted in 5.76 lost life years per patient and 4.14 lost quality-adjusted life years (QALYs) per patient in China.[18-20]
- In Canada, delays affected 6400 patients, who lost up to 1740 life years and 1122 QALYs (valued at CA$112 million). Productivity loss was estimated at CA$106 million.[21]

Delays have cost healthcare systems millions in lost productivity and economic burden. Patients suffer the most due to higher mortality, financial strain, and reduced quality of life. However, access alone isn't enough. We need to ensure successful implementation and continuously evaluate real-world impact.

An Academia Perspective

Further data show considerable differences in the time to access and implications for patients: An analysis of 167 EMA-approved drugs (2019-2022) revealed a European Union (EU) average of 474 days from EMA approval to market access, with significant variations between countries—Germany having the shortest access time (47) and Poland (770) among the longest.[22] Analysis from Canada showed prolonged time from proof of efficacy to first public funding, resulting in considerable years of life lost (**Figure 4**).[19]

A variety of options are available to improve the access of patients to innovative medicines:

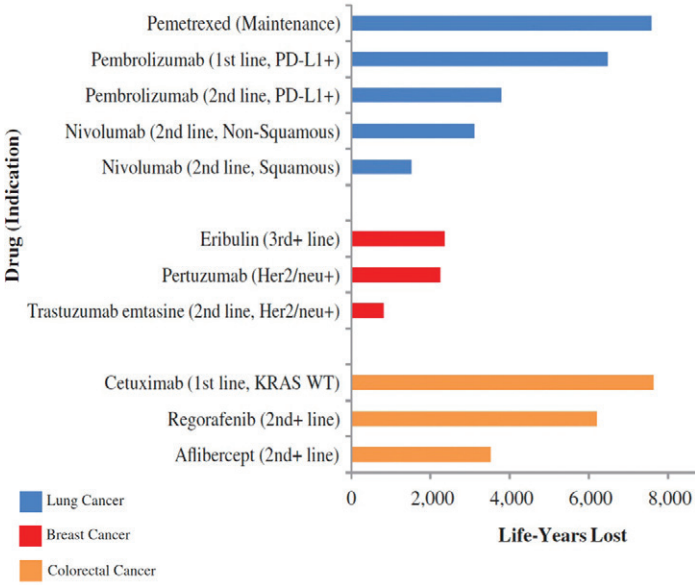
- Optimizing early access schemes: France reshaped its Early Access schemes in 2021 with 3 routes of Compassionate Use Authorization (CUA), Early Access Authorization (EAA), and Direct Access (DA) with different timings in relation to marketing authorization. In addition to the benefit of having early access to treatment, an analysis showed that majority of medicines included into the early access scheme turned into Service Médical Rendu (SMR) important assessment later.[23,24]
- Accelerating regulatory timelines: Project Orbits is an initiative with global regulatory reach through which countries can benefit from the usually earlier submission to the US Food and Drug Administration (FDA). It was launched by the FDA's

Figure 3. Representation of categories when measuring the impact of delays in access to treatment in oncology

Impact category	Description	Examples
Direct costs	❖ Treatment-related costs ❖ Resource-use costs ❖ Adverse-event related costs	✓ More chemotherapy cycles ✓ Higher rate of hospitalizations ✓ More symptom treatment medications
Indirect costs	❖ Productivity losses - patients return to work later and caregivers lose wages ❖ Other indirect impact	✓ More absenteeism, presenteeism, premature-mortality ✓ Travel-related costs, financial strain on family
Health impact	❖ Deterioration of health outcomes	✓ Additional LY lost ✓ QALY burden ✓ Increased adverse events caused
Healthcare system costs	❖ Increased demand on limited resources	✓ More demand for social care ✓ More terminal care cost due to increasing deaths ✓ Admin costs related to prolonged HTA/ delays
Wider impact	❖ Wider impact on the society and patients	✓ Patient anxiety and distress ✓ Financial toxicity ✓ Social Isolation and reduced community participation

Abbreviations: HTA, health technology assessment; LY, life year; QALY, quality-adjusted life year.

Figure 4. Delay from proof of efficacy to health technology assessment process to first public funding[19]



Oncology Center of Excellence in 2019, and it seeks to expedite patient access by coordinating regulatory reviews across multiple countries, including the United States, United Kingdom, Australia, Brazil, Canada, Israel, Singapore, and Switzerland. As an example, this approach has significantly reduced regulatory timelines in Switzerland, reducing the submission gap from 168 to 33 days and median review times from 314 to 235 days.[25]

- Alignment of HTA requirements: In Europe, an overhaul of HTAs through the introduction of the Joint Clinical Assessment (JCA) through the EU HTA Regulation aims to standardize evaluations across member states and therefore accelerate access to medicines. However, this might be possible only in the mid- to long-term, whereas in the short-term it might increase the burden and delay processes. The experience was similar at the time of the introduction of the EMA.[26]
- Deletion of the fourth hurdle: A final example of how to potentially speed up access to cancer medicines is by revisiting the so-called fourth hurdle, which refers to having access to medicines only after completion of the HTA. In Germany, access is immediately granted at the start of the respective HTA rather than after its completion, leading to the quick access to medicines in Germany as shown in some of the above-mentioned analyses.[22]

Conclusions

Delays in oncology treatment access can have measurable consequences: impacting survival, quality of life, and healthcare system efficiency. While progress has been made, disparities remain. A multistakeholder approach is essential to accelerate access, supported by early evidence generation, aligned HTA and pricing processes, and adaptive policy reforms. Timely access isn't just a regulatory goal—it's a necessity for delivering the full value of innovation to patients, health systems, and society.

Ultimately, the benefits of therapeutic improvements in oncology, often with life-saving potential, should be available for patients without delay.

The ISPOR Oncology Special Interest Group (SIG) was established to identify new trends and methodological challenges in oncology HEOR with the intent of supporting education, awareness, and community engagement while working towards the development of recommendations to address them. The SIG aims to advance clinical and methodological knowledge for proper clinical and economic evaluation of oncology treatments and diagnostic tools. This article reflects the key ideas presented by the authors during the group's recent webinar on delayed access to cancer treatments.

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June 18 | 10:00AM – 11:00AM EDT

Negative Control Outcomes in Observational Studies of Effectiveness

This webinar will focus on the use of negative control outcomes as a mechanism to evaluate confounding before embarking on a comparative analysis. Brought to you by the ISPOR Statistical Methods in HEOR Special Interest Group.

July 8 | 10:00AM – 11:00AM EDT

Global Standards, Real-World Impact: The Role of HARPER

This webinar will cover the recent International Council for Harmonization guidance which establishes international standards for planning and conducting real-world data studies for regulatory submissions. It will also cover the Centers for Medicare and Medicaid Services guidance on using real-world evidence to support coverage determinations. Brought to you by the ISPOR Real-World Evidence Steering Committee.

July 10 | 10:00AM – 11:00AM EDT

AI in Evidence Synthesis: Are the Robots Taking Over?

Artificial intelligence (AI) has rapidly become a key component of healthcare decision making; however, can it replace the human touch? In this webinar experts will discuss the science and sentiments around implementing AI capabilities, including how they are perceived by stakeholders. Brought to you by ISPOR Corporate Partner, OPEN Health.

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HEOR ACROSS THE GLOBE

ASIA PACIFIC

Section Editor: **Paula Lorgelly, PhD**, Auckland, New Zealand

Editor's Note:
Value & Outcomes Spotlight is pleased to introduce "HEOR Across the Globe" as a recurring section in the magazine. The Section Editors work with a small team of Regional Reporters from Asia Pacific, Latin America, and Eastern Europe, Middle East, and Africa to cover developments in health policies, news, and events from these regions.

The Impact of the Trade War on the Medicine Supply and Pricing: Australia's PBS Faces Scrutiny

Jing Jing Li, Centre for Health Economics, Monash University, Australia

Australia's Pharmaceutical Benefits Scheme (PBS), a cornerstone of the country's universal healthcare system since 1948, is facing renewed scrutiny amid escalating trade tensions with the United States.

In early 2025, US President Donald Trump reiterated plans to impose tariffs on countries that, in his view, benefit from lower pharmaceutical prices at the expense of American innovation. Australia, with its cost-effectiveness–based PBS pricing model, was explicitly named in this context. Industry groups in the United States have echoed these concerns, labeling Australia's approach as unfair trade practice.

While no tariffs have yet been implemented, the threat has raised concern among health policy observers. Tariffs on pharmaceutical imports or pressure through trade negotiations could make it more costly or commercially less attractive for manufacturers to supply medicines to Australia. This may result in delayed access to new treatments or added budget pressures for the PBS.

The PBS relies on centralized procurement and economic evaluation to ensure value for money and broad access. If US tariffs increase costs for global manufacturers or reduce the commercial attractiveness of the Australian market, consequences may include delays in accessing new treatments or rising prices.

These developments coincide with other US pharmaceutical pricing proposals, including the recently announced reference pricing, linking US prices to those in peer countries. This was widely discussed at the ISPOR meeting in Montreal as the executive order was signed just days before the meeting. While it is aimed at domestic (United States) reform, such policies may have global pricing impacts, particularly if companies respond by raising prices in lower-cost markets or delaying their launches in those countries.

The Australian government has responded by reaffirming its position: the PBS will not be part of any trade negotiations. Nonetheless, growing alignment between trade and pharmaceutical policy internationally suggests this issue will warrant ongoing monitoring to ensure Australia's access and affordability objectives remain secure; this will be true for all countries in the Asia-Pacific and elsewhere that effectively employ economic evaluation methods to price technologies so they deliver value-for-money.

Disclosure: Jing Jing Li, through Monash University, has a contract with the Australian Government Department of Health and Aged Care, providing independent evaluations of company submissions to the Pharmaceutical Benefits Advisory Committee (PBAC) for listing on the Pharmaceutical Benefits Scheme (PBS).

Broader Value Assessment in HTA Decision Making for the Asia Pacific: ISPOR Singapore Chapter BRAVER Report Launch

Carsten Schousboe, Roche; **Zhiyu Qiu**, ISPOR Singapore; **John Cheong**, Roche; **Aaron Jason Martin**, MSD; **Alec Morton**, National University of Singapore

An Office of Health Economics report, *"Beyond Health: The BRAVER Roadmap to Broader Assessment of the Value of Health Interventions in the Asia Pacific Region,"* commissioned by Roche, MSD, and J&J, explores health technology assessment (HTA) practices across Asia-Pacific (APAC). The report explores the integration of broader value elements into regional HTA frameworks, on the premise that adopting a more comprehensive perspective is necessary for advancing healthcare decision making beyond traditional clinical and cost metrics. It recommends HTA bodies to incorporate wider societal impacts and patient-centered outcomes in their assessment methodologies.

On 26 May, the ISPOR Singapore Chapter organized a launch event bringing together key HTA stakeholders to introduce the report and discuss broader value recognition in local practice. The event focused on the need for APAC HTA frameworks to evolve beyond clinical and direct cost assessments to capture indirect costs like productivity losses and caregiver burden.

The BRAVER report observes that while APAC HTA frameworks are strong in evaluating clinical effectiveness and direct costs, they often lack mechanisms to capture broader societal outcomes. This limitation creates an opportunity for regional HTA bodies to evolve their methodologies while maintaining their foundational strengths.

Professor Alec Morton (National University of Singapore) opened the event, acknowledging that many of the directions in the BRAVER report resonated with key Singapore policy priorities (eg, protecting the workforce, taking care of the worst off, and ensuring efficient operation of the health system). He outlined opportunities for learning from his research and other jurisdictions, especially The Netherlands, United Kingdom, and Nordic countries in making these concepts operational. Carsten Schousboe (Roche) offered insights from New Zealand's experience with adopting broader value assessment and the progress Canada is making, addressing methodological, political, and ethical concerns in adopting a societal perspective.

Polling at the launch showed strong support for incorporating novel value elements into Singapore's HTA, although readiness to model them was lower. Participants proposed solutions to improve readiness by having more open discussions with the Agency for Care Effectiveness and the Ministry of Health, as well as hosting multistakeholder workshops and training on societal perspectives in modeling.

The report and launch event represent an important step towards more holistic, patient-centered healthcare evaluation across APAC.

HEOR ACROSS THE GLOBE

EASTERN EUROPE, MIDDLE EAST, AND AFRICA

Section Editor: **Bertalan Németh, PhD**, Budapest, Hungary

Toward HTA in Oman

Said Wani, MSc, Semmelweis University, Budapest, Hungary

Healthcare decisions are complex, especially in a scarcity of resources scenario, where the trade-off between available choices becomes a necessity. Aligning with Oman Vision 2040, the implementation of health technology assessment (HTA) has become one of the priorities of the Ministry of Health, in order to enhance the evidence base for decision making and use available resources more efficiency.

The journey of HTA in Oman begins with drawing a roadmap to analyze the gap between the current and future status of HTA implementation. This goal was determined through the engagement of stakeholders and decision makers. The implementation roadmap outlines a 10-year phased approach and 8 domains: (1) Capacity building, (2) Funding, (3) Legislation, (4) Scope, (5) Decision criteria, (6) Quality and transparency, (7) Use of local data, and (8) International collaboration. In the short run, the roadmap focuses on capacity building through training, initial funding models of HTA, evaluating high-impact pharmaceuticals, and developing decision criteria.

In addition, the long-run strategy aims to integrate HTA into academic programs, bordering HTA coverage scope to other ranges of healthcare technologies such as prevention programs and ensuring the publication of recommendations.

In April 2025, the Ministry of Health launched the methodological guidelines of HTA. This is one of the important steps to improve the evidence base of policy decisions. The guidelines provide a standardized and transparent approach to judge the value and affordability of health technologies, aligning with international best practices and local healthcare needs and priorities. It consists of 6 sections, including targeted indication, medical assessment, economic evaluation, budget impact analysis, social and ethical considerations, and transparency requirements. As per the guidelines, economic evaluation assessments will use cost-utility analysis for any technologies with health gain, expressed in incremental quality-adjusted life years (QALYs), and cost-minimization analysis for technologies with no health gain to the comparator.

Also, Oman cost-effectiveness thresholds have been developed. The baseline threshold is linked to gross domestic product (GDP) per capita and complemented by multipliers that account for priority disease setting, rarity, and health gain. The willingness to pay for a QALY gain in Oman cannot exceed 1x GDP per capita for new health technologies with minor health benefits in common diseases. However, based on health policy priorities, the maximum threshold value can be increased up to 12x GDP per capita for a QALY gain in case of curative medicines for rare cancer diseases.

Oman cost-effectiveness thresholds align with the broader societal perspective, allowing for a higher willingness to pay for technologies addressing rare diseases to promote equity, prioritizing areas like cancer with unmet medical needs, and valuing interventions that offer QALYs improvements. Through a phased roadmap, tailored cost-effectiveness thresholds, the launch of a national methodological guideline and critical appraisal checklist, Oman is laying the groundwork for a sustainable HTA framework that supports national health priorities. The strategy is to establish a single centralized HTA unit under the Ministry of Health.

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Hungary Hosts Key Regional Congress

Bertalan Németh, PhD, Budapest, Hungary

The 13th Adriatic Congress of Pharmacoeconomics and Outcomes Research took place in Budapest, Hungary this year. It was the first time that Hungary was selected as a host of the annual event, and the Hungarian ISPOR Chapter took a pivotal role in organizing the Congress, in close collaboration with the team of permanent organizers. The 3-day congress was attended by experts both from Central, Eastern, and Western European countries, and a representative from Oman.

Among many illustrious guests, ISPOR's Chief Science Officer, Laura T. Pizzi, PharmD, MPH, was among the participants. Laura's presence and involvement at the Congress further emphasized the importance of the EMEA region to the Society. She served as a panelist to discuss how to incorporate the societal perspective in HEOR analyses. She also engaged in strategic discussions with ISPOR's regional leaders to further strengthen the collaboration between ISPOR and its chapters. The SUSTAIN-HTA project workshop was organized as a satellite event of the Congress. Here, Laura took part in discussing HTA methods implementation and sustainability approaches. In addition to attending the Congress, Laura also visited 2 Hungarian universities and met with HTA and Health Policy experts in the region.

Section Editor: **Diego Rosselli, MD**, Bogotá, Colombia

Regulating Risk-Sharing Agreements: A Key to Accessing Innovative Therapies

Magda V. Gutiérrez, MD, Director, ISPOR Chile Chapter, Bogota, Colombia

In Chile, access to innovative medicines constitutes one of the primary barriers to ensuring effective treatments for the entire population, particularly for individuals facing high-cost diseases. In this context, risk-sharing agreements (RSAs; ARC in Spanish) emerge as a pivotal solution. These agreements enable pharmaceutical providers and healthcare systems to share financial risks associated with the efficacy or utilization of specific medicines. However, the effective implementation of such agreements necessitates progress in establishing a clear and consensual regulatory framework.

Regulating RSAs would yield benefits for patients, insurers, and providers—fostering access to cutting-edge therapies through a sustainable financial model. Moreover, it would help reduce health inequalities by enabling access to costly treatments for those most in need without compromising the financial stability of the healthcare system.

The recent Exempt Resolution 410, issued by the Minister of Health, which approves the technical guidelines for the implementation of risk-sharing agreements, marks a significant step toward achieving this goal in the country. This technical framework lays the foundation and pillars to develop and apply RSAs transparently and efficiently. Such progress positions Chile closer to ensuring equitable access to innovative medicines, thereby benefiting thousands of patients and enhancing the sustainability of the healthcare system.

Mexico Tightens Drug Sourcing Rules Amid Global Trade War

Diego Rosselli, MD, EdM, MSc, Pontificia Universidad Javeriana, Bogotá, Colombia

The trade war started by the Trump administration has significantly impacted its neighbor, Mexico. As extensively debated in the media, President Trump's vision of bringing back home manufacturing processes currently done abroad will likely have many predictable and unpredictable consequences. Surprisingly, in April, Mexican President Claudia Sheinbaum announced a similar measure for her country, set to begin in 2026.

Her proposal targets pharmaceuticals and medical devices purchased by any government agency, including the vast *Instituto Mexicano de Seguro Social* (which covers roughly half of Mexico's 130 million citizens), the military, Pemex (the national oil company), and all healthcare programs for the uninsured. Only providers with a manufacturing plant in Mexico would be considered.

The predicted consequences of this measure will likely affect high-tech biopharmaceuticals, many of which are produced in only 1 or 2 plants worldwide, as well as biosimilars and generics from large Asian manufacturers. While stimulating local pharmaceutical production might seem appealing, simple ideas may not always be the best solution.

If you have ideas for a story or want to contribute an update, please email voseditor@ispor.org.

METHODS EXPLAINED

In this edition of Methods Explained, we are covering discrete choice experiments based on a conversation with Janine van Til and Verity Watson. Janine van Til, PhD is an Associate Professor in health preference research at the department of Health Technology and Services Research of the University of Twente in The Netherlands, and active member of the ISPOR Special Interest Group on health preferences research and the Internation Academy of Health Preference Research. Verity Watson, PhD is a Senior Economist at RTI Health Solutions and Honorary Professor at the Health Economics Research Unit of the University of Aberdeen in the United Kingdom.

Discrete Choice Experiments

Section Editor: **Koen Degeling, PhD**

What are discrete choice experiments and what can they be used for?

Discrete choice experiments (DCEs) are part of the group of stated preference methods. They are based on several ideas about how people make decisions between competing options. The first principle is that people always choose the option with the highest perceived value in choosing between products or services. Second, people value the attributes of the options rather than the options themselves, and their preferences are based on the desirability of those attributes. Third, people are willing to trade (ie, accept) negative outcomes on certain attributes to obtain positive outcomes on others.

Within the field of health economics and outcomes research, DCEs are primarily used to understand the relative importance of attributes of alternative health or healthcare options (eg, health states, treatments, healthcare services), and the trade-offs people are willing to make between them. This has several use cases, including the assessment of benefit-risk trade-offs, for example in regulatory decision making, the assessment of the willingness to pay for different benefits, and health state evaluation. They can also be used in implementation science to understand what is important when introducing a healthcare service, or during development to understand the potential benefit of a new intervention.

Although DCEs have been typically used to understand preferences on a group level, they can be used to understand variation in preferences within a certain patient population (ie, preference heterogeneity). For instance, this can help to identify subgroups of patients who are willing to accept a higher risk to achieve higher benefit from treatment. Finally, DCEs have been applied on an individual level to support patients in deciding between treatment options by helping them to understand what is important to them.

On a practical level, how do DCEs work?

As a prerequisite, it should be possible to describe the (range of) healthcare products or services of interest using attributes, with each attribute having different levels that describe the possible outcomes. For example, when considering a medicinal product, attributes can be the effectiveness (eg, probability of 5-year survival), risk of a severe adverse event (eg, the proportion of patients experiencing the event), and mode of administration (eg, oral or intravenous). When evaluating a healthcare service, attributes can be the time spent with a healthcare provider (eg, in minutes), type of healthcare provider (eg, doctor or specialist nurse), and the travel distance to see the provider (eg, in kilometers or miles). Extensive qualitative research is needed to appropriately describe the options, their attributes, and the levels of these attributes.

Different combinations of attribute levels are generated using experimental design methods, aiming to cover the entire spectrum of options within a manageable number of questions. In each question, study participants are presented with 2 or more hypothetical options described by the attribute levels and asked which option they would choose, typically through a survey. In a typical study, participants answer between 8 and 16 questions. An example of what such a question may look like is presented in the **Figure**.

Several outputs are obtained from analyzing the responses to a DCE survey. First of all, the relative importance of the attributes is obtained. This is a measure of the influence of each attribute on the preference for the options. Second, one can obtain the marginal rate of substitution that gives information on the extent to which people are willing to trade outcomes between

Figure. Illustration of a hypothetical discrete choice experiment.

Which health service would you choose?

	Select the service you prefer	
	Health Service A	**Health Service B**
Specialist providing the care	Doctor	Specialist Nurse
Duration of the appointment	10 minutes	30 minutes
Waiting time for the appointment	8 days	2 days
Travel distance to the appointment	20 km	5 km
I prefer …	☐	☐

2 attributes. This can be used to determine the willingness to wait for an appointment to talk to a doctor (see example above), but likewise, it can be used to estimate the willingness to pay, the maximum acceptable risk for a certain benefit, or the minimum required benefit that is needed to offset a certain risk. Finally, the preference share can be obtained. This can be used to assess the uptake of a certain health intervention or service given the alternatives in the market and give insight in how changing certain attributes of an intervention is expected to impact uptake.

What makes DCEs different from other preference research methods?
There is a fundamental difference between stated preference research, for which DCEs are used, and revealed preference research. The latter is based on choices that have been observed in practice. These are a more reliable estimate of actual choices but come with 2 important limitations: (1) no understanding is obtained of why people made a certain choice, and (2) the findings are limited to the options available in practice at the time of the decision, which may be different from those of interest. DCEs address these limitations.

> In the end, the relevance of findings is determined by the representativeness of the participant sample to the research question and, hence, careful consideration should be given to the dissemination of the survey.

Another method that comes to mind to address these limitations may be interviews. However, the value of interviews to understand preferences that are representative for a patient population is often limited by the sample size and the inherent selection of the participants. Rating scales and similar survey questions are often used to understand the importance of attributes or to elicit direct preferences for healthcare products or services. However, these types of questions do not incorporate trade-offs, making their findings less valid for understanding what drives the preferences and the value of health and healthcare from a methodological perspective.

One may also compare DCEs to multiple-criteria decision analysis (MCDA). While DCEs are used to understand why people have certain preferences, MCDA aims to assist people in making more (rational) decisions. Eliciting the relative importance that people attach to certain attributes that drive these decisions is an important step in an MCDA, and the relative importance of attributes, as derived from a DCE, could be used for this.

What are the steps in developing a DCE?
After defining the research question and doing formative research to identify what drives people's choices, the most important step in designing a DCE is describing the options using attributes and levels. One needs to balance the number of attributes that is feasible in terms of participant burden, while ensuring that all attributes that are relevant to the decision are included. Like any survey, a DCE should be designed with care and extensively pilot tested to ensure that participants' understanding of the attributes and instructions is correct. In the end, the relevance of findings is determined by the representativeness of the participant sample to the research question and, hence, careful consideration should be given to the dissemination of the survey.

To what extent are DCEs being used and what challenges remain?
DCEs are used in regulatory decision making to inform benefit-risk trade-offs. The US Food and Drug Administration has guidelines on how to perform stated preference research, including DCEs, which includes recommendations on how to incorporate the findings in the regulatory process. The European Medicines Agency does not have specific guidelines for the latter but has endorsed multiple project groups in performing methodological work.

In terms of health technology assessments, the number of applications with clear impact on reimbursement decisions remains low. However, there are some examples where a DCE provided information that was considered in the decision making of agencies. For example, the Pharmaceutical Benefits Advisory Committee in Australia has considered results from a DCE in their decision making, albeit with several caveats.[1]

One of the important limitations of DCEs as a stated preference methodology is that it remains unknown whether the respondent would actually make the decision that is predicted by their stated preferences. However, there is an increasing body of literature that provides insights into the consistency of stated and revealed preferences. Another challenging aspect of DCEs is balancing the scope of the experiments in terms of the number of attributes and levels, the efficiency of the survey, and the cognitive burden to the participants. Experience of the researchers is instrumental in striking the right balance.

This edition of *Value & Outcomes Spotlight* focuses on Alzheimer's disease. Are there specific considerations regarding DCEs in this disease area?
As current treatment options for Alzheimer's disease offer relatively modest incremental benefits, DCEs can be very helpful in assessing the benefit-risk trade-off for these treatments. Quality of life is very important to patients with Alzheimer's disease, so it is important to know what trade-offs they are willing to make to give them the best possible life they have in front of them. DCEs may also provide insights that can be used to inform the design of healthcare services for patients, as well as supporting services for caregivers.

Carefully considering the design of DCEs becomes even more important in the context of Alzheimer's disease, because keeping the survey as simple as possible is critical to enable patients to participate as their disease progresses. This is a delicate balancing act, as one wants to give a voice to patients with decreased cognitive function, but at the same time wants to avoid asking them to carry out tasks that are too complex. If patients themselves are not able to complete the DCEs, their caregivers can complete them on their behalf as proxies.

What are some key references for further reading?
For those wanting to read one or more case studies, Morrish et al recently identified 9 studies of DCEs in Alzheimer's disease.[2] For those interested to learn more about how to perform DCEs, ISPOR Task Force groups have published several guidance papers on DCEs,[3,4] as well as a more recent perspective on increasing the usefulness and impact of patient-preference studies.[5]

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We welcome your feedback on this article and any suggestions for methods to be covered in future editions. Send your comments and suggestions to the *Value & Outcomes Spotlight* Editorial Office.

FROM THE JOURNALS

The Excess Direct Social Costs of Dementia-related Neuropsychiatric Symptoms: A Regionwide Cohort Study Beyond Silos

Zumeta-Olaskoaga L, Ibarrondo O, del Pozo R, Zapiain A, Larrañaga I, Mar J. *Value Health*. 2025;28(4):536-544.

Section Editor: **Agnes Benedict**, Executive Director, Thermo Fisher Scientific, PPD Evidera Health Economics & Market Access
Contributor: **Paulina Kazmierska**, Thermo Fisher Scientific, PPD Evidera Health Economics & Market Access

The behavioral aspects of Alzheimer's disease are less well-known to the public. These neuropsychiatric symptoms (NPS) include irritability and depression, agitation, apathy, among others—and in the worst cases, motor disturbances, hallucinations, delusions, and disinhibition. These often represent the earliest signs of the disease, posing a source of stress for patients and a substantial challenge for caregivers of dementia patients, which can lead to institutionalization.

In their recent article published in *Value in Health's* themed section, The Health Economics of Alzheimer's Disease and Related Dementias, Zumeta-Olaskoaga et al. aimed to quantify direct nonhealthcare costs disaggregated by the presence of dementia and associated NPS. To this end, the authors performed a retrospective cross-sectional study using electronic health records (EHRs) from health and social care databases of the entire cohort aged 60 and above (n=215,859) in the Gipuzkoa province in Spain.

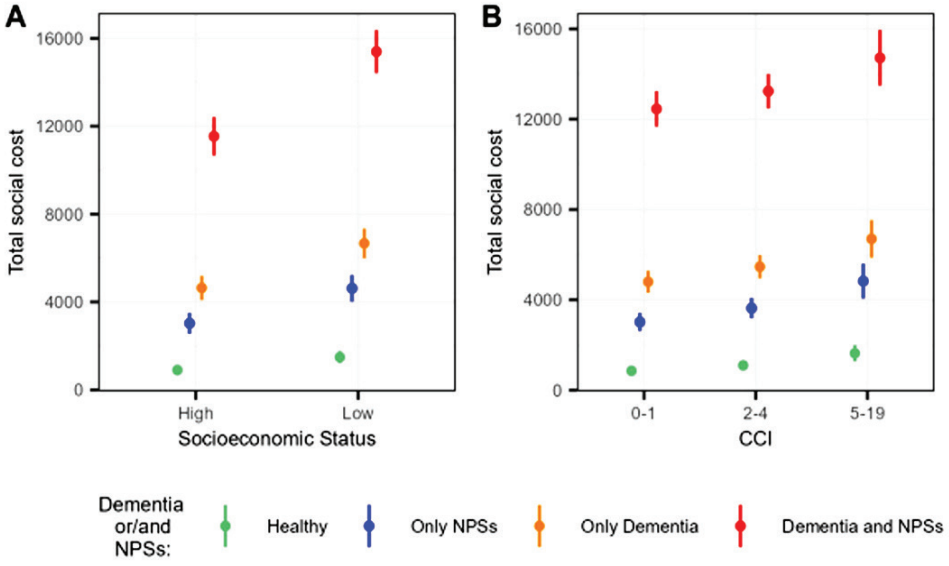
Given the inadequate coding of NPS in EHRs, the authors used previously developed machine-learning-based algorithms to identify NPS in EHRs based on data on comorbidities and prescribed medications. Direct nonhealthcare costs were defined as the costs of formal services such as residential care centers, day/night care centers, and home help services, as well as cash benefits regardless of their funding (in Spain, part of these costs are financed through copayments, with levels varying by income). Entropy balancing accounted for differences in demographic, clinical, and socioeconomic variables between groups with and without dementia.

The annual costs were calculated based on cash benefits plus product of benefits in natural units each individual received and unit costs. Two-part regression models were used to estimate excess social costs associated with NPS and dementia. The first part estimated the odds of incurring any costs at all (versus none), and the second part used a regression to estimate the mean cost when the cost was higher than zero. Together, the 2 models could be used to estimate average costs for different combinations of covariates. In addition to dementia, NPS, and their interaction, the models included age, sex, Charlson Comorbidity Index, and socioeconomic status.

Among the cohort studied, 3.5% of individuals had dementia, 34.7% had NPS, and 9.6% received dependency benefits. The results showed that dementia and NPS are independently associated with substantially greater odds of incurring direct nonhealthcare costs (odds ratios of 7.36 and 3.23, respectively), but NPS in the presence of dementia does not further increase the odds of incurring such costs.

Both dementia and neuropsychiatric symptoms are also associated with higher social costs, when incurring any (ie, nonzero), and NPS in the presence of dementia leads to additional excess annual costs (ranging from €4161 to €14,929, depending on the reference category). The authors also report that lower socioeconomic status (**Figure 1A**), higher Charlson Comorbidity Index (**Figure 1B**), and older age are associated with higher direct nonhealthcare cost.

Figure 1. (A) Mean of the estimated total costs and average of the upper and lower confidence limits of these estimates for each population group by socioeconomic status and (B) Charlson Comorbidity Index.



CCI indicates Charlson comorbidity index; NPS, neuropsychiatric symptoms.

The study provides valuable results as it quantifies the indirect financial impact of dementia and NPS. It highlights how the Spanish long-term care system actually mitigates some of the inequality, since the burden of NPS seems to be greater among patients with low socioeconomic status.

Some limitations apply. The results are specific to the region in which the study was conducted. Cost estimates are not adjusted for the severity of dementia (as EHRs lack this level of granularity of clinical data). Analysis of uncertainty stemming from the use of unit costs would be a valuable addition.

However, study results provide critical inputs to analyses establishing the burden of dementia and NPS and the interventions' value for money that target dementia and NPS (in Spain, specifically). The study can also serve as a blueprint for similar studies in other jurisdictions.

Editor's Note:
The April 2025 issue of *Value in Health* featured a special collection of papers on The Health Economics of Alzheimer's Disease and Related Dementia. The themed section includes an introductory editorial by the Guest Editors, Thomas Rapp and Pei-Jung Lin, and 8 full-length articles.

You can read the themed section here.

EC EDITOR'S CHOICE

The Editors-in-Chief of *Value in Health* and *Value in Health Regional Issues* select papers from each issue that they believe will be of high interest to readers. Below is a sample of a few of their recent selections, which are freely available to read to everyone. **ENJOY!**

Value in Health

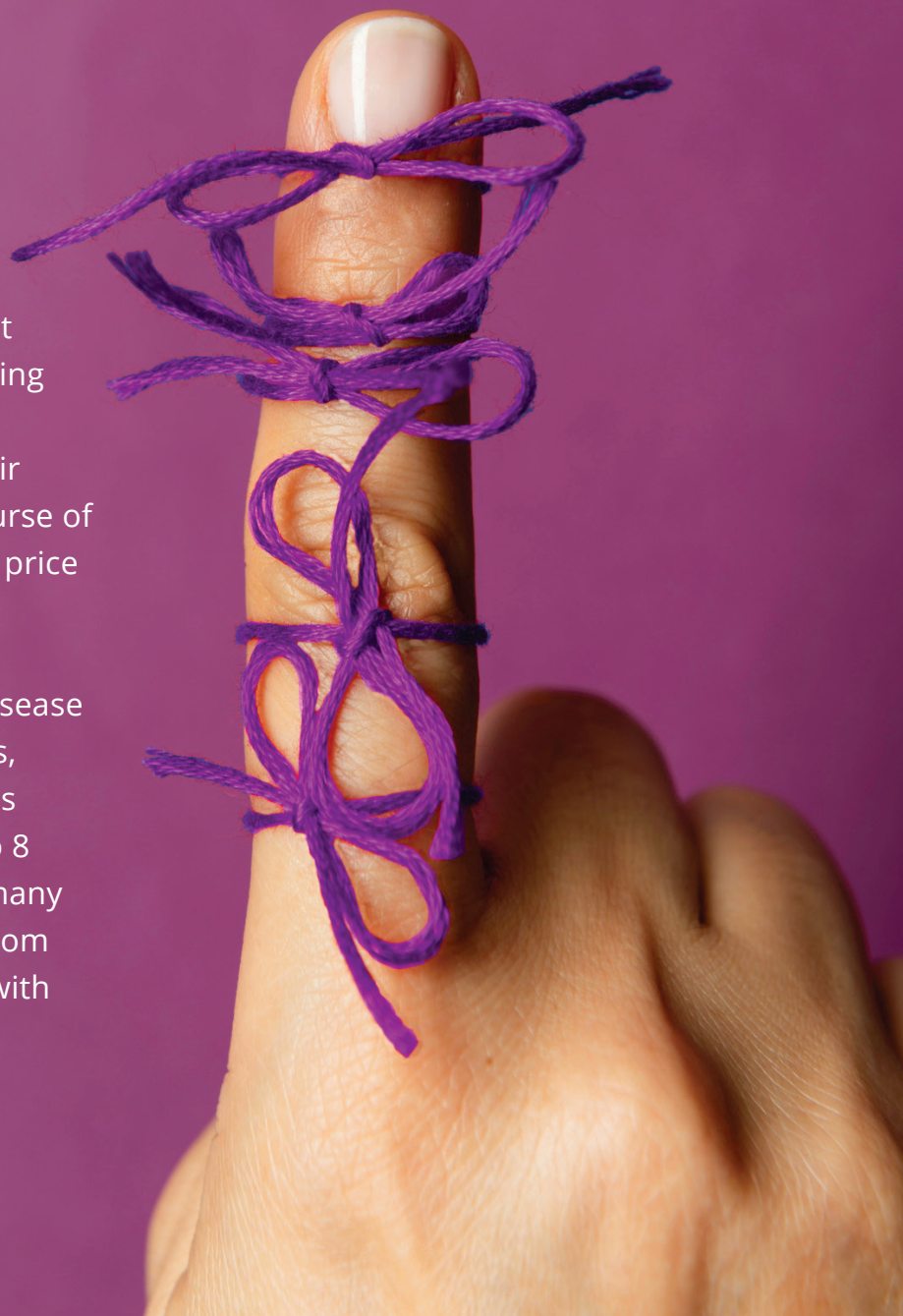
- Taking HEOR Forward: Expanding the Definition of Value to Include Whole Health
- The Price Effects of Biosimilars in the United States
- Cost-Effectiveness of a Digitally Supported Care Management Program for Caregivers of People With Dementia
- How Do Bundled Payment Initiatives Account for Differences in Patient Risk Profiles?

Value in Health Regional Issues

- Toward Better Measurement of Financial Risk Protection in Health Expenditure
- Comparing the Measurement Properties of the EQ-HWB and EQ-5D-5L in Patients and Caregivers
- Efficiency Analysis of Healthcare Systems in Latin American and Caribbean Countries
- Economic and Disease Burden of Multiple Sclerosis in Colombia

Tied to the Past, Unprepared for the Future: Meeting the Alzheimer's Disease Challenge With HEOR

BY BETH FAND INCOLLINGO



There has been a lot of fanfare about the first 2 medicines capable of slowing the progress of Alzheimer's disease, lecanemab and donanemab, but their costs over a typical 1.5- to 2-year course of treatment can easily rival the sticker price for the average new car.

Yet, without the ability to slow the disease during its earlier symptomatic stages, how much more would society pay as these patients required an extra 6 to 8 months of round-the-clock care, in many cases preventing family caregivers from continuing to work and spend time with their children?

At the other extreme, if Alzheimer's disease (AD) could be prevented or treated before symptoms developed, how much would that burden drop, and what level of investment in public education, research, and medical care would be warranted to make it happen?

As AD cases spiral, experts in health economics and outcomes research (HEOR), health technology assessment, policy, science, and advocacy are at odds about how to respond cost-effectively—and even about the importance of that effort.

Each year, dementia costs the world more than $1.3 trillion US dollars, half funding medical treatment and nursing-home fees and the other half constituting care provided at no charge but often significant sacrifice by loved ones, according to Paola Barbarino, CEO of Alzheimer's Disease International (ADI), the federation of AD and dementia associations around the world.[1] That investment is likely to grow quickly, as the number of people with AD is expected to nearly double every 20 years.[1]

A reluctance to shoulder more of that burden could explain why many governments limit their engagement with AD, the most common form of dementia, Barbarino said.

Yet, advocates believe it's crucial for governments to increase their commitment to raising awareness about AD and its proven preventive measures while supporting more timely diagnosis so that a broader swath of patients will be eligible for the new drugs. Supporters are also calling for increased scientific funding so that research programs can expand to match the scope of the problem. While nearly 40% of the world's pharmaceutical research and development efforts are centered around the development of cancer treatments, dementia gets a much smaller piece of the pie.[2]

The bottom line, many advocates agree, is that AD isn't getting the attention it deserves.

"There are as many people with neurodegeneration as with cancer, but there's a huge underinvestment in neurodegeneration," said Bart De Strooper, MD, a group leader at the UK Dementia Research Institute at University College London and a 2018 winner of the Lundbeck Foundation Brain Prize for his research into the mechanisms underlying AD.

"If you go to PubMed, where the world's scientific publications are compiled, there are 5 million papers about cancer but only 400,000 about neurodegeneration," De Strooper continued. "Yet, there are equal numbers of cancer patients—55 million in the world versus 58 million people with dementia. So, there's really something not right here."

Barbarino believes that imbalance arises, in part, from bias.

"The attitude of payers seems to be that these people are old, and that giving them an extra 6 months won't mean much," she said. "Yet, you wouldn't say that in cancer, would you?"

A Misunderstood and Underrecognized Condition

Globally, 65% of healthcare professionals and 80% of the public wrongly believe that dementia is a part of normal aging,[3] Barbarino said, and that view is often coupled with the misconception that meaningful intervention is impossible.

Responsible for 60% to 70% of dementia cases, AD is driven by biological changes that cause otherwise healthy proteins to accumulate in the brain, manifesting as amyloid plaques and neurofibrillary, or "tau," tangles.[4] These built-up proteins kill cells and cause the brain to shrink, resulting in progressive memory loss, personality changes and, ultimately, death—unless disease-related infection or aspiration pneumonia become fatal first.[5]

ADI's goals are to improve risk reduction, timely diagnosis, care, and inclusion while working toward a cure for the disease.[6]

To support prevention, ADI promotes educational campaigns and government interventions focused around 14 risk factors that, if modified, can reduce the risk of AD by 45%: less education in early life; hearing loss, high LDL cholesterol, depression, traumatic brain injury, physical inactivity, diabetes, smoking, hypertension, obesity, and excessive alcohol use in midlife; and social isolation, air pollution, and visual loss in late life.[7]

Each year, dementia costs the world more than $1.3 trillion US dollars. That investment is likely to grow quickly, as the number of people with Alzheimer's disease is expected to nearly double every 20 years.

"I do not see a huge amount of uptake of the kind of campaign that would make the public aware of that—although countries like Canada have done it," Barbarino said. "Then, there's still a lot of work needed to understand how to get people to change their behaviors."

To make matters worse, she said, on average, 75% of the world's dementia cases are never diagnosed, and that proportion rises to 90% in some low- and middle-income countries, where stigma is more pronounced.[8]

As a result, Barbarino said, "85% of people living with dementia are not accessing any form of post-diagnostic support,"[9] which could otherwise include:

- Nonpharmaceutical rehabilitative strategies like brain and physical exercises, wearable health monitors, home modifications, and skill building for family caregivers[10]
- Medical treatment in the disease's early symptomatic stages with 1 of the 2 drugs on the market or therapy at various stages with more than 125 compounds being tested in clinical trials[11]

- Treatment at more advanced symptomatic stages with drugs like memantine hydrochloride, which slow the processes that damage neurons and are often paired with cholinesterase inhibitors, which improve nerve cell communication to ease memory loss

As most patients live 3 to 11 years after diagnosis,[12] an unmitigated battle with the disease can be not only grueling but expensive, De Strooper noted.

The Potential of Alzheimer's Treatments

Also misunderstood is the promise of lecanemab and donanemab, said De Strooper, whose prize-winning research contributed to the development of the drugs by shedding light on a trigger of the disease cascade—the abnormal production of amyloid due to genetic mutations. The infused drugs work by clearing the brain of amyloid plaques.

As of March 2025, lecanemab (Lequembi; Eisai and Biogen) had been approved in the United States, South Korea, China, Japan, Israel, Hong Kong, the United Arab Emirates, Macau, and Mexico, but was largely unavailable in Europe. Meanwhile, donanemab (Kisunla; Eli Lilly) had received the green light in the United States, China, and Japan.[12]

> To make matters worse, 75% of the world's dementia cases are never diagnosed, and that proportion rises to 90% in some low- and middle-income countries, where stigma is more pronounced.

Many decision makers complain that the medications don't delay AD for long, are expensive, and come with side effects, including a 35% rate of ARIA — a brain edema or bleed that can cause headaches or dizziness but typically no other symptoms, De Strooper said.[13] Severe brain bleeds occur in less than 1% of patients and cause death in 0.2% to 0.3%, he said.[14,15]

In a 2023 report, the Institute for Clinical and Economic Review—an independent, nonprofit US organization that compares the value of proposed interventions against that of existing alternatives—found that lecanemab was not cost-effective at its list price of $26,500 per year, citing its mild slowing of cognitive loss versus the risks of ARIA.[16]

Nevertheless, De Strooper believes regulators should support the use of such drugs and offer fast-track approvals—as they often do when reviewing cancer treatments—because anti-amyloids have the potential to radically change the trajectory of AD. The goal, he said, should be to offer them to affected patients as long as 2 decades before symptoms appear,[17] while also refining eligibility requirements.

Early treatment could become more feasible, he said, as clinics gain access to diagnostics like Lumipulse, which recently became the first blood test for AD to be approved by the US Food & Drug Administration.[18] In the United Kingdom, a clinical trial is assessing diagnostic blood tests for dementia with the hope of eventually administering them before patients develop symptoms.[19]

"If you treated patients before they had already lost neurons, you could make the amyloid disappear before it triggered the other steps and have a much bigger effect," De Strooper said. "There are already some preliminary data in patients suggesting that."

Stopping the formation of amyloid plaques and tau tangles before irreversible brain damage occurred, he said, could make it possible to transplant memory-restoring neurons into the hippocampus of affected patients; that technique is already evolving as a treatment for Parkinson's disease.[20]

He added that the ability to stop the disease presymptomatically could open the door to additional novel therapies that could be used in concert with anti-amyloid drugs. His ongoing research on the role of genetics in AD could help make that possible.

"If we don't get rid of the taboo atmosphere and fatalism surrounding AD and allow these anti-amyloid drugs to enter the market, doctors won't be able to do clinical trials testing them in earlier treatment," De Strooper said. "Also, by approving these drugs, we'll create a market around them that will be in place when better antibodies come out, such as small-compound formulations that can be taken as pills, and that will enable competition."

While scientists at Harvard University are using artificial intelligence to determine whether existing drugs might work against AD,[21,22] De Strooper said he doesn't expect that research to produce miracles.

"These efforts should not take away from the hardcore basic research, screening, and testing that has been successful in any other field," he said.

Considering Investment

Despite those arguments, many governments remain reluctant to invest, which is why the World Health Organization's global action plan on the public health response to dementia has not been fully executed, Barbarino said.

While Japan and South Korea have put together large budgets to help cope with AD, she said, the United Kingdom—where dementia is the biggest killer in absolute terms—has continually postponed plans to boost its dementia care resources.

Government leaders often tell Barbarino they can't afford to devote additional funding to AD, and one country's representatives falsely claimed the disease didn't exist there.

That lack of commitment often results in loved ones providing care, which takes them away from their jobs, schools, and families and tends to leave them more isolated, which can negatively affect their mental health. In higher-income countries, inadequate support drives up emergency department visits and nursing-home stays. Alternatively, in low- and middle-income countries, where migration is widespread, Barbarino said, people with dementia often have no family or pensions to help them and end up dying alone, sometimes sadly in the street.

Barbarino also said, "Currently many countries experience a loss of workforce in the crucial years, in which caregivers are caring for parents with dementia and for children," Barbarino said. "Better respite care and support provision would enable people in this situation to continue working and providing for their families."

> As the world's decision makers grapple with the cost of Alzheimer's, HEOR experts can guide them by determining where the bulk of funding should be directed to produce the best outcomes.

Policy makers can consider how proposed investments in AD care would play out by using HEOR-based algorithms that predict outcomes, said Eric Jutkowitz, PhD, an associate professor of health services, policy, and practice at Brown University. His team has created a microsimulation that predicts dementia progression and associated costs at the population level, available as a tool for leaders in government, health plans, and hospital systems.

Another strategy for cost-effectiveness is to strategically coordinate existing AD resources, and the United States is one of several countries to have introduced such an effort. On July 1, 2024, the United States launched an 8-year pilot test of its Guiding an Improved Dementia Experience (GUIDE) Model, which uses standardization to support quality of life for eligible Part A or B Medicare recipients who don't participate in Medicare Advantage, along with their unpaid caregivers.[23]

Being offered by 390 longstanding providers and a growing spate of new physician groups, all of which receive value-based payments for their efforts, the program is intended to help patients stay in their homes and communities while reducing strain on unpaid caregivers through education, access to a 24-hour support line, assistance in finding community-based providers, and up to $2500 per year in respite care services.[24]

"Coordinating these services instead of providing them individually represents a huge shift in how healthcare systems are thinking about providing care to people with dementia," Jutkowitz said. "There's an increased emphasis on using evidence-based models."

Still, because global AD support remains a patchwork, 120 groups affiliated with ADI are working to fill unmet needs by providing care and support groups, funding or participating in research, urging policy makers to boost services, and monitoring governments as they roll out their plans.

Unfortunately, Barbarino said, "There are many countries where we cannot work because of a conflict or mistrust of civil society, and a denial of the existence of dementia."

A Global Commitment

As the world's decision makers grapple with the cost of AD, Jutkowitz said, HEOR experts can provide guidance on the allocation of resources.

Of course, De Strooper would like to see a significant portion of that funding go to medical research, and he believes supporters can help by mobilizing a grassroots approach, as did advocates for the AIDS community in the 1980s.

"AIDS was also a terrible disorder that was seen as taboo, and patients were too occupied to do anything about it," he said. "But after initial drugs had little effect, friends and colleagues of those patients went to industry and the government and successfully pushed for more research."

Continued support for AD research will remain just as crucial, he said, especially as the United States, which historically led this effort, considers cutting the budget of its National Institutes of Health by 40%, among other policy changes restricting scientific investigation.[25-27]

"In the richer countries, we need to develop and use Alzheimer's drugs and give industry an appetite to make more," De Strooper said. "Then, governments, social networks, and patients need to demand treatment for everybody so we can think about how to bring these medications to the rest of the world."

While Barbarino agrees that investment in research is essential, she would like to see decision makers diversifying their focus in an effort to execute all 7 areas outlined in the WHO's Global Action Plan. In addition to research and innovation, those action areas are: dementia as a public health priority; dementia awareness and friendliness; dementia risk reduction; dementia diagnosis, treatment, care, and support; support for dementia carers; and information systems for dementia. "Dementia is an all-of-society issue, and without funding in each of those areas, we will not achieve true progress toward dementia action," Barbarino said.

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Further Reading:
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By the Numbers: Alzheimer's Disease

Section Editor: **The ISPOR Student Network**
Contributors: **Kanya K. Shah**, University of Illinois Chicago, Chicago, IL, USA; **Khaled Alamri**, University of Cincinnati, Cincinnati, OH, USA; **Jennifer Contreras**, University of Maryland, Baltimore, Baltimore, MD, USA; **Daniel Ojonugwa Umoru**, Chapman University, Irvine, CA, USA; **Godwin Okoye**, University of Texas at Austin, TX, USA; **Dominique Seo**, University of Maryland, Baltimore, Baltimore, MD, USA; **Shayma Mohammed Selim**, Queensland University of Technology, Brisbane, Australia

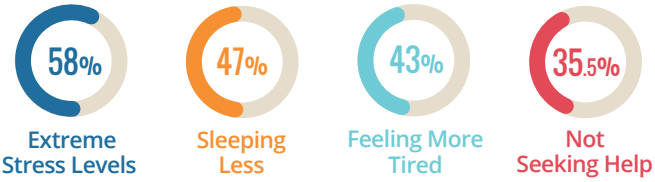
Caregiver Burden in Alzheimer's Disease and Related Dementias

11.9 MILLION unpaid caregivers working ~31 hours per week

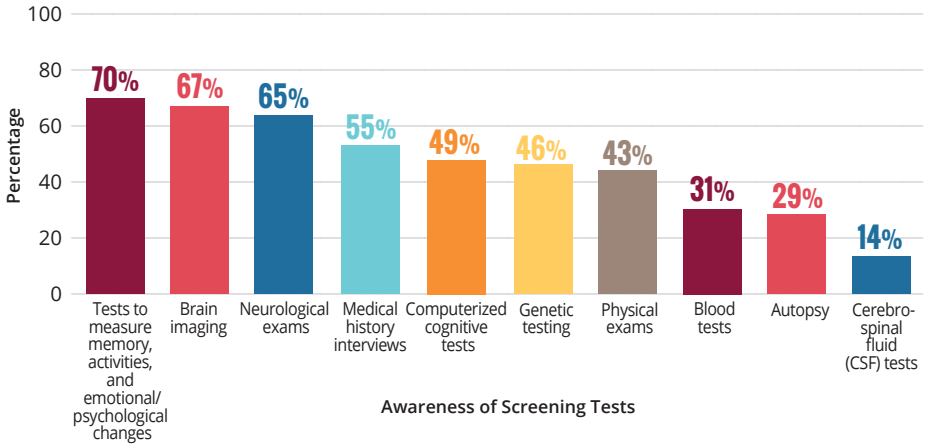
CREATE **19.2 BILLION** uncompensated work hours

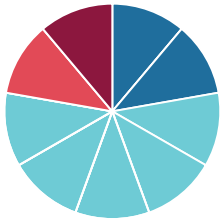
WHICH CREATES **$413.5 BILLION** of unpaid care provided in the United States in 2024 (assuming minimum wage rates)

CAREGIVERS REPORT...



Diagnosis and Treatment for Alzheimer's Disease





9 DRUGS ARE APPROVED FOR TREATING ALZHEIMER'S DISEASE

- 2 of these drugs **change the underlying biology** of Alzheimer's disease and **slow cognitive and functional decline** in some individuals.

The remaining drugs **treat the symptoms** of Alzheimer's dementia.

- 5 treat cognition/functional symptoms
- 1 treats behavioral symptoms
- 1 treats mood symptoms

Screening Tools for Early Diagnosis of Alzheimer's Disease

Mini-Cog
2-part assessment: 3-item recall task and a clock-drawing task

2-3 Minutes

Detects mild cognitive impairments/dementia

Domains:
1. Immediate and delayed recall
2. Visuospatial/executive function

MoCA
Moderately comprehensive assessment

10-15 Minutes

Detects mild cognitive impairments

Cognitive domains:
Attention, concentration, executive functions, memory, language, visuospatial skills, abstract thinking, and orientation

MMSE
Brief cognitive assessment

5-10 Minutes

Alzheimer's disease monitoring and progression

Cognitive domains:
Orientation, registration, attention, calculation, recall, language, and visuospatial skills

MMSE (Mini-Mental State Examination)
MoCA (Montreal Cognitive Assessment)

Global Burden, Emerging Breakthroughs: The Dual Stories of Alzheimer's Disease

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KEY TAKEAWAYS

Alzheimer's disease (AD) and dementia-related diseases represent an urgent global health crisis, affecting 55 million people worldwide, with projections surpassing 152 million by 2050.[1]

While treatments like monoclonal antibodies offer new hope, critical gaps in care coordination and caregiver support persist.

To truly address the profound impact of AD, a multi-faceted approach that combines medical advancements, caregiver empowerment, and system-wide reforms is essential for the future.

With an aging global population and increased awareness driving projected rises in Alzheimer's disease incidence, the societal and economic burdens of the disease are mounting. At the same time, funding uncertainties threaten to stall research progress—underscoring the urgency to seize opportunities for breakthroughs powered by cutting-edge technology and innovation in healthcare.

Introduction

Alzheimer's disease (AD) affects 55 million people worldwide,[2] with its reach extending far beyond those diagnosed to include loved ones and caregivers. With no definitive cure, the number of individuals impacted by AD is projected to soar to over 152 million by 2050.[3] As one of the most feared conditions associated with aging,[4] the consequences of the disease are felt across multiple layers of society—public health, economics, and individual lives.

> As demographic shifts continue, these higher-risk populations are expected to make up more than half of the United States population by 2045, raising concerns about the growing impact of the disease.

As the global impact of AD continues to grow, understanding its broader implications is critical. This piece explores the burden of AD, examining its public health and economic impact, providing an overview of the disease state, reviewing current and emerging treatments, and highlighting critical gaps in the care ecosystem.

Alzheimer's Disease Overview

AD is the most common cause of dementia—the umbrella term for conditions impacting memory, thinking, and social cognition.[5] Approximately 6 million Americans over the age of 65 are affected, and AD accounts for 60-70% of dementia cases worldwide.[2,6] The typical symptoms can include weakening or loss of memory, reasoning skills, language, and spatial understanding, and behavioral/personality changes.[7] As the condition progresses, complications such as a decline in physical health, infections, and loss of control over bodily functions may also happen.[7] While the cause of AD is not known, it likely stems from a combination of genetics, environmental factors, and age.[8] Diagnosing AD requires a complex combination of physical exams, diagnostic procedures, and discussions with the patient and family. Typical medical tests, such as urine or blood analysis, may be utilized to assess other potential medical problems.[9] AD is often diagnosed by a neurologist after a series of examinations of the patient's reflexes, coordination, eye movement, speech, and sensation levels.[10] Symptoms of depression, such as apathy, loss of interest in activities, social withdrawal/isolation, and impaired thinking/concentration, can often overlap with AD and can be difficult to differentiate.[11] Brain imaging with MRI is another standard test used in AD diagnosis to rule out other potential conditions with similar symptoms.[10]

Public Health Impacts, Disparities, and Unmet Needs

The burden of AD and related dementia is increasing, due to the aging global population and persistent health disparities. Although advancing age is the strongest risk factor, newer research suggests the risk of developing dementia may be even higher than previous estimates.[12] But AD does not affect all communities equally. Studies show significant racial disparities, with some minority groups facing a disproportionately higher risk. As demographic shifts continue, these higher-risk populations are expected to make up more than half of the United States population by 2045, raising concerns about the growing impact of the disease.[12] Socioeconomic factors further compound these disparities. Limited access to education and nutrition

may contribute to early differences in cognitive reserve, while inequities in healthcare and a greater burden of vascular risk factors in midlife drive higher rates of AD in marginalized communities.[12]

Despite the growing demand for dementia care, the healthcare system in the United States remains unprepared for the rising AD cases—20 states have been classified as "dementia neurology deserts" due to the severe shortage of geriatric specialists and critical limitations in access to diagnostic and treatment services.[13] Compounding the challenge, the complexity of AD requires a holistic approach addressing physical, mental, and social well-being. Yet, the siloed nature of the healthcare system makes it difficult to provide streamlined, coordinated care, leaving many patients and caregivers without the support they need.[14] These gaps in workforce capacity and care coordination not only strain the healthcare system but also limit patients' access to timely diagnoses and comprehensive support. As the prevalence of AD rises, so does the urgency for effective treatments and interventions. While recent advancements in research have brought new therapies to the forefront, questions remain about their accessibility, efficacy, and long-term impact on disease progression.

> Addressing neuropsychiatric comorbidities associated with AD is a significant unmet need for patients and caregivers.

Safety is a major concern for patients with AD and their caregivers, highlighting an unmet need for support and frameworks to address these issues.[15] Caregivers report uncertainty in dealing with emergencies, managing medications, fall/wander prevention, and avoiding exploitation/fraud.[15] Addressing neuropsychiatric comorbidities associated with AD is a significant unmet need for patients and caregivers. Apathy, agitation, sleep disturbances, aggression, and depression are common neuropsychiatric symptoms accompanying AD.[16] There is a gap in research specific to these symptoms in patients with AD, although the impact is significant. Neuropsychiatric symptoms contribute to increased healthcare expenditure as well as increased burden on healthcare providers and caregivers.[16]

Treatment Landscape

The classes of medications used for AD include cholinesterase inhibitors, NMDA receptor agonists, and monoclonal antibodies.[5] While none of these medications are curative, they can slow disease progression, prolonging quality of life and allowing patients to retain certain levels of independence[17]:

- Cholinesterase inhibitors (donepezil, galantamine, rivastigmine, and others): these drugs prevent the breakdown of acetylcholine, which can help memory and cognition[17]
- NMDA receptor antagonists (memantine): slow the neurotoxicity associated with AD by blocking the NMDAR subtype of glutamate receptors[18]
- Monoclonal antibodies (lecanemab and donanemab): target amyloid-β (Aβ) peptide, tau protein, and neuroinflammation[19]

Additionally, antipsychotics may be used in an off-label capacity to treat behavioral changes associated with the condition.[20]

Caregiver Insights

Caregiving for a loved one with AD and related dementia often extends far beyond a full-time job; it can drastically reshape personal lives. For many caregivers, the emotional and social toll is significant. In fact, nearly half of caregivers reported avoiding social gatherings, fearing how their loved one might be treated by others.[21] Additionally, 41% of caregivers said they refrain from taking vacations, concerned that their loved one would face mistreatment in their absence.[21]

The total annual indirect societal cost of AD increases with severity, ranging from $36,934 for mild cognitive impairment due to AD to $145,250 for severe disease per patient (2024 USD).[22] When factoring in both patient productivity losses and spillover effects to unpaid caregivers, the total annual indirect cost of AD is estimated at a staggering $832 billion.[22] This economic strain underscores the growing impact on caregivers, who often bear much of the financial and emotional weight of the disease.

Amid these challenges, the day-to-day management of AD symptoms presents a substantial barrier, particularly for family caregivers who are often unpaid and lack professional support. However, emerging technological interventions show promise in easing the caregiver burden, offering tools to improve both patient care and caregiver well-being.[23]

Emerging Technologies

Monoclonal antibodies can potentially slow the progression of AD by targeting and clearing amyloid deposits.[24] The most recent FDA approval for an AD drug was for donanemab, a monoclonal antibody treatment.[25] Rather than just addressing symptoms of AD, monoclonal antibodies may slow the cognitive decline associated with the disease.[24] Currently, lecanemab and donanemab are the only FDA-approved monoclonal antibodies on the market for AD.

This evolving approach aligns with a broader shift in AD care toward precision medicine. During a plenary session at the American Academy of Neurology (AAN) Annual Meeting in April 2025, Dr. Reisa Sperling emphasized the importance of tailoring treatments to an individual's genetic and molecular profile. She highlighted how emerging therapies are increasingly designed to target specific pathophysiological pathways, enabling earlier and more personalized interventions.[26] One example of this precision-driven shift is the development of novel diagnostic tools. Research from the University of Cambridge has shown that virtual reality (VR) technology could be used for early AD detection.[27] In a recent study, participants navigated a virtual environment to assess spatial awareness—a cognitive function that can decline years before more noticeable symptoms of AD appear.[27] The use of VR in this context highlights the growing role of technology and personalized assessment tools in identifying AD earlier and more accurately.[27]

A Global Perspective

AD is accelerating into a global health crisis with a projection to reach 82 million patients by 2030.[3] The economic toll is staggering; currently

exceeding US $1.3 trillion annually, it is expected to approach $3 trillion by 2030.[28] Informal caregiving alone accounts for around 40% of this cost, highlighting the profound societal burden of AD.[29]

This burden is not equally shared. In low-income countries, up to 90% of dementia cases go undiagnosed and untreated,[28] reflecting deep disparities in awareness, diagnostic capacity, and access to care. These gaps leave millions without support while reinforcing global health inequities.

> Without coordinated, inclusive action, Alzheimer's disease will continue to strain health systems, families, and economies at an unsustainable scale.

By contrast, high-income countries have adopted innovative models to manage the crisis. Japan leads with dementia-friendly communities and early detection initiatives.[30] Sweden's national strategy emphasizes personalized care and strong caregiver support. The Netherlands excels in integrated, person-centered care coordinated across providers. Luxembourg launched its national dementia plan in 2013 and followed with a prevention program targeting modifiable risk factors.[31]

Still, even the most advanced systems face growing demands. Global progress depends on closing diagnostic gaps, expanding access to community-based care and sharing best practices. Without coordinated, inclusive action, AD will continue to strain health systems, families, and economies at an unsustainable scale.

The Road Ahead

Alzheimer's disease research is facing a major setback as freezes on federal medical research grants prompt sweeping budget cuts and widespread layoffs across key agencies, including the Food and Drug Administration, National Institutes of Health (NIH), Health and Human Services, and Centers for Disease Control and Prevention.[31] This funding halt risks stalling critical progress in treatment development at a pivotal moment. The NIH projects a need for $445 million to meet the 2026 goals of the National Plan to Address Alzheimer's Disease but is currently facing a $113 million shortfall for new research in the upcoming fiscal year.[32]

Compounding the issue, proposed cuts to diversity, equity, and inclusion (DEI) research funding could halt vital studies on women's health.[33] This is particularly significant in the AD space, where women represent nearly two-thirds of all AD and dementia cases.[34] Without continued support for DEI research, efforts to understand how sex and gender differences influence risk factors, disease mechanisms, and progression may be significantly hindered.[35,36] As these challenges mount, the future of AD research and the pursuit of critical breakthroughs remain at a crossroads, with the potential for lasting consequences on treatment development and public health.

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Harnessing Python's Power Beyond AI: Crafting Individual-Level Simulations With the SimPy Library

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KEY TAKEAWAYS

Object-oriented programming (OOP) in Python streamlines the creation and execution of individual-level simulations by representing healthcare entities and processes effectively. Python's simplicity and community support complement OOP, enabling the creation of readable, maintainable, modular simulation models.

Python, alongside its frameworks and libraries like PyTorch, TensorFlow, SciPy, Scikit-Learn, and, most notably, SimPy, addresses challenges in parameter estimation by facilitating data extraction, processing, and validation. This empowers simulations to enhance accuracy and reliability, crucial for effective healthcare system modeling.

Introduction

Modeling in health economics often requires capturing the complex dynamics and interactions of patients, providers, and resources in a healthcare system. Individual-level simulations, also known as microsimulations or individual-based models, are a powerful tool to represent the heterogeneity and variability of patient characteristics, behaviors, and outcomes, as well as the stochasticity and uncertainty of events and decisions. Individual-level simulations enable detailed insights into the performance and efficiency of different interventions, policies, or scenarios, and they help identify potential bottlenecks, trade-offs, and optimal strategies.

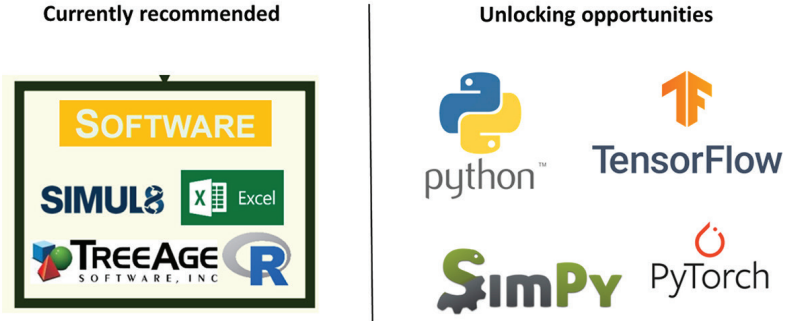
However, individual-level simulations also pose technical and methodological difficulties. Challenges include the need for large and reliable data sources, the calibration and validation of model parameters and assumptions, and the computational complexity and scalability of the models.[1,2] In this article, we discuss how object-oriented programming (OOP) and Python can facilitate the development and implementation of individual-level simulations and overcome some of the limitations identified by the recommended tools (**Figure**).[3]

Object-Oriented Programming for Individual-Level Simulations

OOP is a programming paradigm that organizes data and behavior into reusable units called objects. Objects encapsulate attributes (data) and methods (functions) that define their state and functionality. Objects are instantiation of classes; classes are blueprints or templates for creating objects with the same structure and behavior. Classes can inherit from other classes, meaning that they can extend or override the attributes and methods of their parent classes while still being compatible with code written to handle the parent class. This allows for code reuse and abstraction, as well as capturing both the hierarchical and compositional relationships present between different types of entities.

OOP is particularly relevant for individual-level simulations because it can naturally represent the entities and processes involved in a healthcare system, such as patients, providers, resources, events, and actions. Each type of entity can be modeled as a class, with its own attributes and methods that describe its characteristics and behavior. For example, a patient class can have attributes such as age, gender, diagnosis, and treatment history, and methods such as *generate_event, update_state*, and *record_outcome*. A provider object can have attributes such as capacity, availability, and cost, and methods such as *schedule_appointment, provide_service*, and *collect_fee*. A resource object can have attributes such as location, quantity, and quality, and methods such as allocate, consume, and replenish. Events and

Figure. Comparison between currently recommended modeling software tools (left panel) including SIMUL8, Excel, TreeAge, and R, versus emerging programming frameworks (right panel) such as Python, TensorFlow, SimPy, and PyTorch that unlock new opportunities for healthcare simulation modeling. Adapted from Reference 3.



actions can be modeled as methods that change the state or attributes of one or more objects, or trigger other events or actions. A specific healthcare system can be analyzed in depth. We have implemented basic scripts in which we model a referral system from generalist doctors to specialists, in which bottlenecks causing a long waiting time are created.[4]

> Python, with its seamless integration of object-oriented programming and functional programming paradigms, provides a more user-friendly and versatile experience, bridging paradigms without the complexities seen in R.

Using OOP, patient-level simulations can be built as collections of interacting objects that mimic the real-world dynamics and behaviors of a healthcare system. OOP enables the capturing of common characteristics and variability of different entities, while allowing for specialization and customization of each object or class. OOP enables the uniform treatment of objects of different classes with the same parent class or implementation; by using a technique called *polymorphism*, we can call the same method on different types of patients, providers, or resources with different results for each based on their specific subtype. OOP promotes modularity, readability, and maintainability of the code, as well as facilitating the testing and debugging of the model.

Python for Individual-Level Simulations

Python, a widely used programming language known for its simplicity and versatility, serves as a powerful tool for developing individual-level simulations. Its appeal lies in several key attributes. Python stands out from C++ and Java (both primarily OOP languages) by supporting both OOP and functional programming natively. In contrast, R, while offering object-oriented systems such as S3, S4, and RC, is fundamentally a functional programming language. R's approach to OOP introduces several challenges. Users must navigate multiple OOP systems, each with its own conventions and trade-offs, creating a lack of standardization and interoperability. Systems like S3 are simple but lack encapsulation, while more formal systems like S4 and RC come with steep learning curves and rigid structures. Additionally, performance bottlenecks from dynamic dispatch and limited debugging support make OOP in R less intuitive compared to other languages. Python, with its seamless integration of OOP and functional programming paradigms, provides a more user-friendly and versatile experience, bridging paradigms without the complexities seen in R.

Python has a clear and flexible syntax, which helps developers write code that is brief and easy to understand. This simplicity improves the creation of simulation models that are both graceful and readable, making the development process better. Additionally, the availability of generative AI tools such as ChatGPT or Claude can assist developers, including those less experienced with Python, by providing explanations, debugging support, and generating code based on prompts. However, while such tools can lower the barrier to entry for beginners, it is crucial to emphasize the importance of understanding the underlying logic and assumptions of the generated code to ensure the accuracy and reliability of simulation models. Rather than replacing coding expertise, generative AI serves as a supplementary tool that supports learning and accelerates the development process when used responsibly.

The strength of Python also lies in its vibrant and expansive community of users and developers. This ecosystem contributes to a vast repository of libraries, modules, and frameworks tailored to diverse domains, including scientific computing, data analysis, and simulation modeling. SimPy[5] can be easily integrated with other Python libraries such as SciPy for scientific programming, Pandas for manipulating structured data, Scikit-Learn for machine learning, and Matplotlib for visualizing data.

SimPy "Simulation in Python" is a discrete event simulation framework. SimPy allows defining the entities and processes of a system as objects and creating an environment that manages the simulation clock and the event queue. SimPy also provides features such as resources, containers, and stores, which can be used to model the availability and allocation of different types of resources in a system.

Creating a Simulation

SimPy enables individual-level simulations through a sequence of steps. Start by creating classes and objects that represent different components of the healthcare system—patients, providers, resources, events, and actions. These constructs contain attributes and behaviors that are critical for the simulation's operation.

After laying the groundwork, the next step is to create a simulation environment in SimPy, which serves as the stage for managing time progression and event sequencing. SimPy, as a framework, provides a structured architecture for modeling simulations, unlike standalone libraries that offer specific tools. Within this framework, you define processes—represented as functions or methods—that generate events, influence object states, and trigger subsequent actions.

To set up the simulation, specify initial conditions and parameters, such as patient demographics, resource availability, and event probabilities. As the simulation unfolds, time advances, events occur, and the system's dynamics evolve. Finally, analyze the outputs—like patient outcomes, resource usage, and system performance—using Python libraries to gain insights into the simulated healthcare environment.

Challenges in Parameter Estimation

Python, along with its associated ecosystem, empowers simulations to integrate machine learning and statistical methods, enhancing their ability to process data from diverse sources and estimate parameters for complex models (**Table**). Machine learning, in particular, enables dynamic simulations to achieve greater fidelity by improving parameter estimation and facilitating automated updates with real-time data feeds.[1] This

Table. Relevant Python libraries and their use[6-8]

Python Libraries	Purpose	Example Use Case
PyTorch, TensorFlow, TorchSurv	Designed for machine learning, deep learning, and survival analysis	Building and training neural networks to learn from large datasets, including censored survival data, and to generate predictions or classifications for simulations. For example, predicting patient survival probabilities or time-to-event outcomes in medical studies.
SciPy, Scikit-Learn	Designed for scientific computing classifications	Performing statistical analysis and inference on data, estimating parameters and uncertainty for simulations, and conducting sensitivity analysis or validation tests. For example, estimating probability distributions for hospital stay durations or medication costs.
Pandas, NumPy	Designed for data analysis and manipulation	Handling and transforming data from various sources for simulations. For instance, using data frames or arrays to store, filter, merge, or aggregate data from clinical trials, observational studies, and other sources, and extracting relevant variables or indicators.

synergy ensures that simulations remain responsive to the rapidly evolving nature of information generated by healthcare systems.

Simulations are essential for analyzing healthcare bottlenecks, where demand exceeds supply, leading to delays, inefficiencies, and higher costs. By modeling interactions like event sequencing and resource availability, they offer insights into system dynamics and enable scenario testing. Integrating machine learning enhances these capabilities, supporting dynamic resource allocation in crises and tailoring treatment pathways in personalized medicine. This synergy also addresses challenges like nonlinear data dependencies and complex intervention modeling, unlocking new solutions for healthcare analysis.

As the fields of machine learning and simulation modeling continue to merge,[9] their potential to revolutionize areas such as chronic disease management, epidemiological forecasting, and resource optimization grows, offering profound advancements in healthcare systems analysis.

Lessons Learned

Individual-level simulations are a powerful tool for modeling the complex interactions between patients, providers, and resources in healthcare systems. Python, with its object-oriented programming capabilities and extensive libraries, facilitates the development and implementation of these simulations, offering intuitive ways to represent system entities and processes. It also supports data extraction, parameter estimation, and validation using machine learning and statistical methods, enhancing the accuracy and robustness of simulations. These models can identify bottlenecks and evaluate strategies to address them, aiding in policy and decision-making. To demonstrate this, we have developed a GitHub repository[4] showcasing a simulation of a healthcare bottleneck, illustrating the practical application of these techniques. Furthermore, Python's growing adoption in health economic modeling, as seen in its use for interactive applications like Dash,[10] underscores its relevance for conducting rigorous analyses aligned with health technology assessment methodologies, such as those endorsed by NICE.[11]

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Incorporating Patients Into Open-Source Model Development: A Patient-Centered Approach to Health Technology Assessment

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KEY TAKEAWAYS

Developing open-source models with input from diverse stakeholders, especially patients, ensures transparent and inclusive health technology assessments.

Patient insights are crucial for understanding the patient journey, the value of therapies, and identifying gaps to address in health economic models.

Patient partnership is essential for creating equitable and relevant health economic models. While it may require more resources than traditional approaches, involving patients enhances the model's purpose and value for those it impacts most.

Introduction: Lack of Patient-Centricity in Traditional Health Technology Assessment

Since the 1960s, health technology assessments (HTAs) have been instrumental in guiding healthcare reimbursement decisions.[1] However, HTA has traditionally focused on clinical and economic data, often overlooking the broader needs of patients, caregivers, and other stakeholders directly affected by these outcomes. This exclusion has led to healthcare decisions that often neglect crucial aspects of patients' quality of life and well-being, resulting in policies that do not adequately address their needs.

> Patient preferences, outcomes, goal attainment, and lived experiences should be incorporated into HTA methodologies–shaping research questions, designing models, and integrating evidence–to ensure that assessment models and results truly reflect what patients value.

In recent years, there has been a push to make HTA more patient-centric. International HTA bodies now require manufacturers to include patient preferences in their HTA submissions for market access and reimbursement purposes. These regulatory changes have set the stage for a more patient-centered approach to HTA. For example, organizations like the European Medicines Agency (EMA) and the National Institute for Health and Care Excellence (NICE) mandate patient involvement, recognizing the value of integrating patient experiences and preferences to ensure comprehensive and relevant assessments.[2]

The Concept of Patient-Centered Health Technology Assessment

Unlike traditional HTA, patient-centered HTA establishes a meaningful partnership with patients, families, and caregivers throughout the HTA process. This approach emphasizes coleadership and collaboration with decision makers in strategy, governance, and the review and application of results. Patient preferences, outcomes, goal attainment, and lived experiences should be incorporated into HTA methodologies—shaping research questions, designing models, and integrating evidence—to ensure that assessment models and results truly reflect what patients value.

"Learning laboratories" are needed to test innovative, patient-centered approaches to HTA, including testing methods such as multicriteria decision analysis (MCDA) and goal attainment scaling for incorporating multistakeholder perspectives, including patients with lived experience, in building health economic models. The learning laboratory approach aims to establish best practices for patient centered HTA that can be adopted by various healthcare stakeholders through ongoing evaluation and improvement of these methods.

Incorporating Patient Feedback Into Open-Source Models: Role of Patient Stakeholders

Developing open-source models with input from diverse stakeholders is essential for creating transparent and inclusive HTAs. Active participation from patients, caregivers, clinicians, payers, employers, and other stakeholders helps ensure these models reflect real-world complexities. Engaging patients and caregivers captures crucial patient-centered outcomes and experiences, enhancing decision making and ensuring models remain patient-centered. Ultimately, this approach improves health equity by addressing the needs of diverse populations.

Case Study on a Major Depressive Disorder Open-Source Health Economic Model

To employ an inclusive approach in developing our major depressive disorder (MDD) economic model, we convened a multistakeholder advisory group, including over 20 clinicians, health economists, patients, payers, purchasers, and researchers.[3]

> Patient insights were key to understanding the patient journey, the value of major depressive disorder therapies, and the gaps in research that could and should be addressed in the model.

Over the course of 3 years, the multistakeholder advisory group guided the model scope and design, user interface, input parameters, integration of patient priorities and outcomes, and decision contexts. Their input was instrumental in identifying key variables, outcomes, and real-world applications, making the model more relevant to patients and healthcare decision makers. Patients were financially compensated for their time and input and were kept informed as to how their input changed the development of the model (**Figure**).

During the model development, patient feedback provided greater insight into how the MDD open-source model should be designed to be reflective of the patient journey and to capture aspects of patient preferences in MDD treatment modalities that would support healthcare decision making. Patients directly impacted the MDD open-source model in several key areas:

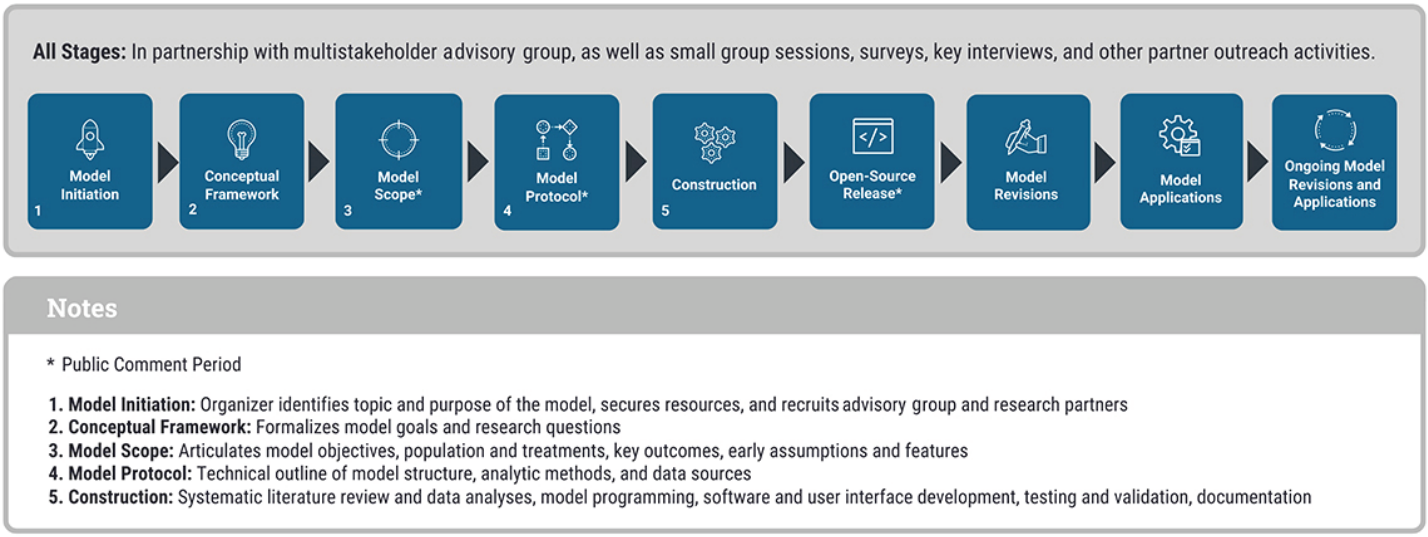
1. Changing the model's focus from treatment-resistant depression to MDD more broadly.
2. Adding additional subgroups to include race and ethnicity.
3. Including additional cost variables (eg, transportation costs, absenteeism, and presenteeism).
4. Designing the user interface to be accessible and user-friendly for technical and nontechnical users, including patients.
5. Incorporating treatment gaps to more closely reflect reality, allowing for periods between treatments when patients receive no care.
6. Expanding outcome measures beyond traditional metrics (eg, life years, quality-adjusted life years) to include outcomes such as time to first response, number of relapses, etc.
7. Modeling relapse as a function of both the degree and timing of the initial treatment response to better mirror real-world experience.
8. Including a placeholder for treatment lines, allowing users to input their own data or test hypothetical scenarios.

Patients also expressed the need to address gaps within the MDD open-source model where further research in MDD is warranted, such as including caregiver burden, societal costs, comorbid conditions such as anxiety, diabetes, and cardiovascular disease, and recognizing health equity issues such as access to care and stigma.

Enhancing Patient Partnership in Health Technology Assessment

Patient insights were key to understanding the patient journey, the value of MDD therapies, and the gaps in MDD research that could and should be addressed in the model. Incorporating patients' feedback was an iterative process, requiring ongoing coordination between patients' and other stakeholders' perspectives. In addition, it was challenging to ensure that we were including diverse perspectives that represented the full spectrum of patients with MDD. We also acknowledge that patient inclusion required additional time and resources during the model development process. However, we believe that the final outputs of the MDD model demonstrate the need for patient perspectives in health economic development. The recommendations below emerge out of our work with patients in developing the MDD model.

Figure. MDD Open-Source Model Development Framework



Abbreviation: MDD, major depressive disorder.

Meaningful Partnership with Patients

Much remains to be done to ensure meaningful patient partnerships. Tools like the National Health Council's Fair-Market Value Calculator[4] and the Center for Innovation & Value Research's Blueprint for Patient-Centered Value Research help formalize processes and ensure that no steps are missed. In the case of the MDD open-source model, patients were included in the model development process from the beginning, acknowledged in the dissemination of the research, and compensated for their time and efforts.

Building Trust With Patient Advocacy Organizations

Ongoing partnerships with patient advocacy organizations are invaluable for HTA. These partnerships aim to strengthen relationships with existing organizations and to engage a broader and more diverse range of patients and patient advocacy groups. For the MDD open-source model, Mental Health America[5] was a key partner, supporting efforts including advising on the multistakeholder advisory group, identifying stakeholders such as patients and patient representatives, supporting dissemination efforts of the model, and advocating for the model's importance for both patients and healthcare decision makers.

Challenges in Identifying and Involving Patients

Unrepresented patients, such as those not affiliated with formal organizations, are often excluded from the HTA process. Challenges in engaging these patients include limited patient networks, communication barriers, and fear of judgment or stigma. Additionally, trust issues may arise when patients feel their voices are not genuinely valued by researchers. When establishing the multistakeholder advisory group for the MDD open-source model, clinicians and patients were the hardest to identify. It was important to cultivate an environment where patients felt safe enough to share their experiences without feeling tokenized.

Importance of Diverse and Representative Patient Involvement

HTA should focus on clinical, financial, quality-of-life, and equity issues. It should reflect diverse patient preferences, goals, and outcomes, and note where patient subgroups are lacking data and implications for decision makers. In the MDD open-source model, patients expressed the need to include inputs that reflected patient subgroups, such as race and ethnicity, adjust for patient heterogeneity, and include additional costing variables.

Need for Understandable and Accessible Explanatory Materials

Most patients and organizations are unfamiliar with HTA. Therefore, it is recommended that accessible explanatory materials be developed, that HTA researchers be trained in patient engagement and communication, and that jargon and specialized terminology be avoided. During the MDD open-source model development process, the multistakeholder advisory group was provided a glossary that included plain language definitions of technical concepts used in the MDD open-source model. During the model-planning sessions, the research team used plain language, thoroughly explained technical aspects of the model, and provided several opportunities for clarification.

Continuous Engagement and Communication

"Closing the loop" on communication fosters active relationships, enabling patients to see how their input is used and its importance in healthcare decision making. Our MDD open-source model development featured continuous engagement during the multistakeholder advisory group meetings, public comment periods, workshops, and dissemination process, which allowed patients to inform and be informed about the HTA process.

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Polypharmacy and Appropriateness of Prescription Medication Among Community-Dwelling Older Adults

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KEY TAKEAWAYS

Polypharmacy, potentially inappropriate medication use, and underutilization of recommended medication are important issues in older adults.

Deprescribing is a promising intervention to reduce polypharmacy but needs to engage multiple stakeholders to effectively implement it in clinical practice.

Implications

Polypharmacy and suboptimal use of medication are prevalent among older adults. Interventions such as deprescribing hold promise for addressing these challenges by optimizing medication use. Effective implementation of deprescribing in clinical settings requires the engagement of multiple stakeholders.

Introduction

As the global population ages and the burden of noncommunicable diseases rises, older adults frequently require multiple medications, increasing the risk of polypharmacy. Polypharmacy, typically defined as the simultaneous use of 5 or more medications, is a significant risk factor for adverse drug events. It is linked to increased risk of drug–drug interaction, frailty, impaired cognitive function, and even mortality.[1] Addressing unnecessary polypharmacy is crucial for promoting quality of medication use and healthy aging among older adults.

> In the shift toward value-based care, reducing unnecessary polypharmacy in older adults is essential for delivering cost-effective and beneficial healthcare.

Beyond its impact on health, unnecessary polypharmacy represents a substantial waste of medical resources. It contributes to increased healthcare utilization and costs.[2] Estimates suggest that 0.3% of global total health expenditure could be avoided with proper management of polypharmacy.[3] In the shift toward value-based care, reducing unnecessary polypharmacy in older adults is essential for delivering cost-effective and beneficial healthcare.

In this recently published study,[4] we provided contemporary nationally representative estimates of polypharmacy and appropriateness of medication use among older adults in the United States and identified specific subgroups that are vulnerable to suboptimal medication usage, highlighting the need for interventions.

Research Methodology

This study used data from the National Health and Nutrition Examination Survey (NHANES), a comprehensive and nationally representative survey of noninstitutionalized residents in the United States. We analyzed data spanning from the 2011-2012 survey cycle to the 2017-2020 cycle. NHANES collects self-reported data on prescription medication use over the previous 30 days, allowing us to delve into patterns of medication usage, therapeutic classes, and the prevalence of polypharmacy.

Key definitions and metrics were as follow:

1. Polypharmacy: the concurrent use of 5 or more medications.

2. Hyper polypharmacy: the use of 10 or more medications.

3. Potentially inappropriate medication (PIM): assessed based on the 2023 Beers Criteria, which identify medications that pose higher risks than benefits for older adults.

4. Appropriate medication use: evaluated against clinical guidelines for heart failure and albuminuria:

1) Heart Failure: adherence to American College of Cardiology/American Heart Association guidelines recommending angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) and beta-blockers.

2) Albuminuria: compliance with Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommending ACEIs or ARBs.

Recognizing that patient characteristics may influence both number and appropriateness of medication use, we reexamined the above estimates by subgroups. Subgroups were defined by sociodemographic characteristics (age, sex, race, marital status, education, income, and insurance) and comorbidities (cardiovascular disease, diabetes, chronic kidney disease, and memory problems).

Results

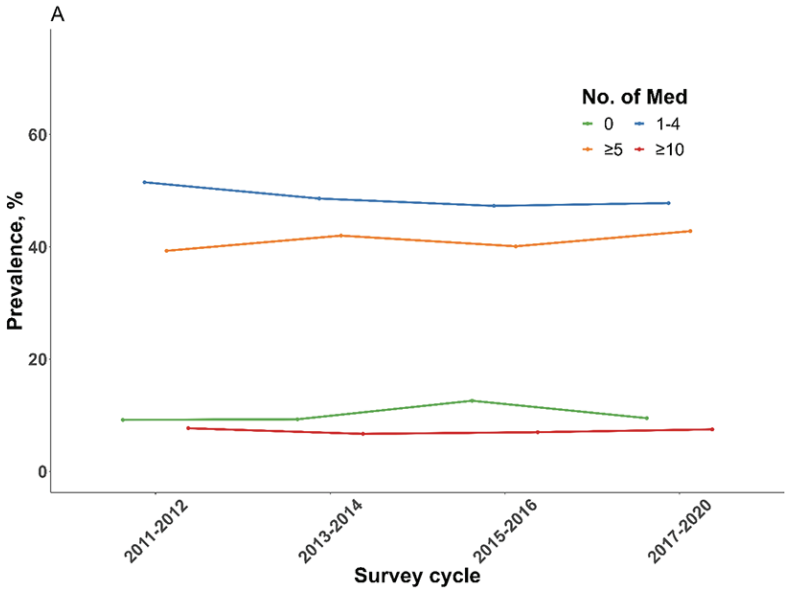
The study analyzed data from a sample of 6336 older adults, with a mean age of 72.9 years, and 55.8% of whom were female. From 2011 to 2020, the mean number of medications used by older adults increased slightly from 4.1 in 2011-2012 to 4.4 in 2017-2020. The prevalence of polypharmacy rose from 39.8% in 2011-2012 to 43.8% in 2017-2020 (**Figure 1**). Meanwhile, approximately 8% of older adults had hyper polypharmacy. Participants of older age, married or living with a partner, with higher body mass index (BMI), and with comorbidities were more likely to have polypharmacy. Notably, over 60% of older adults with memory problems were affected by polypharmacy.

In older adults, cardiovascular drugs were the most commonly used medications, with 68.3% using them in 2017-2020. Among these medications, 65.5% used antihypertensive medications. Metabolic drugs were the second most commonly used class, with 52.4% of patients using lipid-lowering medications and 22.7% using glucose-lowering medications. Central nervous system drugs were the third most commonly used category, with 16.3% using analgesics and 13.2% using anticonvulsants.

Potentially inappropriate medication use

The use of at least 1 PIM decreased slightly from 17.0% in 2011-2012 to 14.7% in 2017-2020. PIM use was more prevalent among individuals aged 80 years or above, females, non-Hispanic whites, those with Medicare plus Medicaid, and those with comorbidities. Polypharmacy was associated with higher likelihood of PIM use: 27.0% of older adults with polypharmacy reported PIM, and the most commonly used inappropriately were central nervous system drugs.

Figure 1. The prevalence of polypharmacy among community-dwelling older adults in the United States from 2011 to 2020.



Appropriate medication use

For patients with heart failure, only 44.3% used the recommended ACEI/ARBs and beta-blockers. In patients with albuminuria, 54% used recommended ACEI/ARBs. Over the past decade, there has been no significant improvement in the appropriate use of these recommended treatments. Older age, female, living without a partner, having Medicare and Medicaid, and lower income were generally associated with lower likelihood of receiving appropriate medications. Among those with polypharmacy, only 46.8% of patients with heart failure and 67.1% of those with albuminuria received recommended treatment.

Discussion

In this analysis of a nationally representative sample of community-dwelling older adults, we found that the quality of medication use has not improved in the past decade. Issues like polypharmacy and PIM remain prevalent, while the utilization of recommended medications for conditions such as heart failure and albuminuria is alarmingly low. Our results underscore the need to enhance the quality of medication management for older adults and emphasize the urgency for better implementation of targeted interventions to address these ongoing issues.

Our study confirmed that polypharmacy continues to be a common issue among older adults. The complexity of polypharmacy is further compounded when considering the appropriateness of medication use. Our data indicate that many commonly used medications among older adults may be inappropriate, with only a slight reduction in the proportion of individuals using PIMs over the past decade. Alongside of inappropriate medication use, it is crucial to make sure that critical medications with proven clinical benefits are not underprescribed. Our data showed that fewer than 50% of older adults with heart failure and only slightly more than 50% of patients with albuminuria used guideline-recommended medications. Even among patients with polypharmacy, guideline-recommended medications were underprescribed. This underprescription can lead to significant adverse outcomes, such as mortality. The findings suggest that a balanced and comprehensive approach to medication management is needed—one that addresses both the reduction of unnecessary medications and the promotion of essential, beneficial treatments.

One promising strategy to address unnecessary polypharmacy is the practice of deprescribing.[5] This approach involves reviewing patients' medication regimens to taper, stop, discontinue, or withdraw drugs that may no longer be necessary or appropriate. Deprescribing emphasizes patient-centered care and shared decision-making, aiming to

manage polypharmacy and improve health outcomes (see **Figure 2**).

Research supports the benefits of deprescribing, including reduced medication use, decreased PIM prevalence, and improved medication adherence. Additionally, deprescribing can lower medication costs and reduce waste.[6] Economic evaluations indicate that deprescribing interventions for community-dwelling older adults are often cost-effective and, in 85% of cases, cost-saving.[7] However, the evidence regarding its impact on broader outcomes such as all-cause mortality, fall prevention, hospitalization, and quality of life is less consistent.[6]

Despite its potential, implementing deprescribing in clinical practice faces significant challenges. Barriers exist at multiple levels—patient, provider, and systemic. The Deprescribing Research Network has developed a socioecological model that categorizes these barriers into individual, interpersonal, organizational, and societal levels.[8]

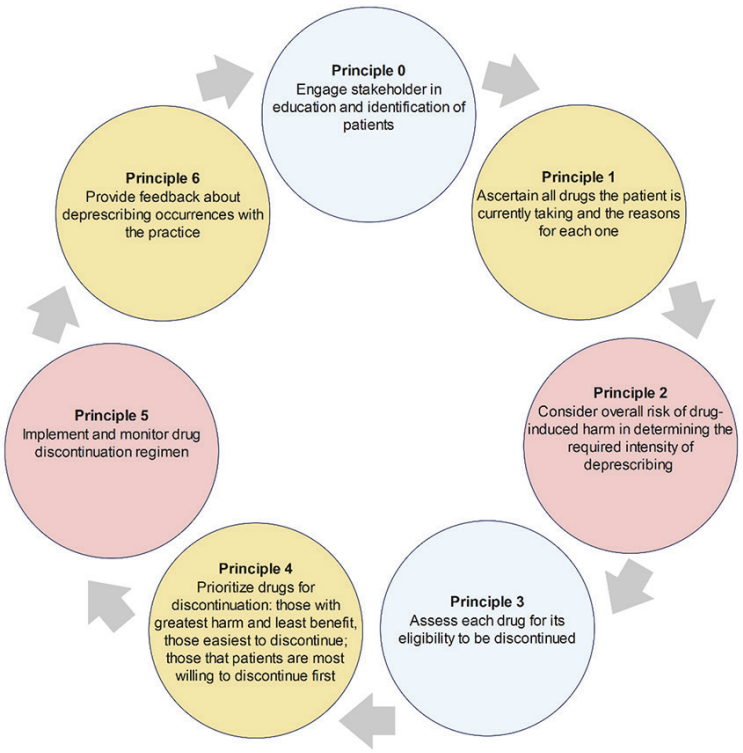
> Research supports the benefits of deprescribing, including reduced medication use, decreased PIM prevalence, and improved medication adherence.

Common obstacles include a lack of knowledge and training about deprescribing processes, limited time, fear of adverse consequences, resistance from patients and their caregivers, and the fragmentation of the healthcare system.[9] To overcome these barriers, a multidisciplinary and collaborative approach with effective communication is essential.

Conclusion

In summary, our systematic examination of medication use among older adults over the past decade highlights persistent challenges. Polypharmacy, the use of PIMs, and the underutilization of recommended medications continue to be significant issues. Our findings emphasize the need for targeted interventions that engage multiple stakeholders, including healthcare providers, patients, and policymakers, to effectively implement deprescribing and improve the quality of medication management in this vulnerable population.

Figure 2. The practice process of deprescribing among community-dwelling older adults



Disclaimer:

This article is a summarized version of the author's previously published work and is intended for the readers of Value & Outcomes Spotlight. It does not replace the original publication which is available at: Pan S, Li S, Jiang S, et al. Trends in number and appropriateness of prescription medication utilization among community-dwelling older adults in the US: 2011-2020. J Gerontol A Biol Sci Med Sci. 2024;79(7):glae108. doi: 10.1093/gerona/glae108.

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This Technology Should Be Compared With?... And for Whom? The Digital Health Population Conundrum

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KEY TAKEAWAYS

Digital health technologies (DHTs) can have a wide scope in terms of population, comparators, and implementation and therefore should be evaluated as such.

A one-size-fits-all approach to evaluation of DHTs may hinder the ability of decision makers to make informed decisions.

Background

Health interventions delivered through digital technologies, such as smartphones, web-based resources, and text messaging, have become increasingly common over the past decade. Such digital health technologies (DHTs) can be used for treatment, diagnosis, data analysis (scanners and monitors), and for improving system efficiencies.[1] As DHTs become more popular and their efficiency improves, they will begin to augment or replace traditional healthcare interventions. Therefore, economic evaluation studies are of central importance for making informed decisions about DHTs. However, DHTs present methodological challenges for economic evaluation, which have been observed with other healthcare interventions, but are more common for DHTs.

DHTs can often be used across a wide range of pathways, rather than in the treatment of specific health conditions. Consequently, a DHT may change the existing processes or pathways of care, which can create difficulties in finding the relevant comparator in economic evaluation.[2] The comparators may also differ at local, regional, and national levels, particularly where a DHT is replacing part or all of a face-to-face care pathway. Thus, it is important to consider the comparator used in economic evaluation of a DHT and to build in flexibility for this to be easily adapted to more local settings.

A second challenge for economic evaluation is the difference in population indication for interventions. DHTs may be used on a wide-ranging population, rather than being defined by the therapeutic indication, as is usually the case with pharmaceuticals. Although DHTs share similar features to medical devices on the indicated population, they are still even more likely to be used across a wider range of indications than medical devices. For example, a DHT may be used across all people suffering with chronic pain, whereas a medical device may only be used for specific types of pain. Hence, understanding how the population may vary needs to be taken into consideration when evaluating a DHT.

Health economic evaluation can be used to highlight the impact of investment in DHTs while facilitating efficient use of limited resources. However, economic evaluation applied inconsistently or illogically—such as not using the most appropriate comparator or population—can hinder the decision-making process.

> Digital health technologies may be used on a wide-ranging population, rather than being defined by the therapeutic indication as is usually the case with pharmaceuticals.

This article aims to describe how these issues can be approached when evaluating the health economic impact of DHTs. Along with this, the paper will discuss other potential challenges, including the implementation of DHTs into the National Health Service.

Our Approach

A pragmatic literature review was undertaken to find research that had sought to provide clarity or had outlined a framework for the evaluation of DHTs. This was conducted using unstructured searches on PubMed and Google Scholar. Extraction focused on frameworks that identified issues and/or solutions associated with either appropriate populations or comparators for DHTs.

Following this, a series of expert panel discussions and interviews were undertaken whereby the approaches to evaluating DHTs, including the approach to capturing the population and selecting the relevant comparators, were discussed. The interviews were informed by the pragmatic literature review so that we could determine if the experts agreed or disagreed with the published literature.

The discussions and interviews captured people with a range of experience, including health economic consulting as well as academic and public sector perspectives.

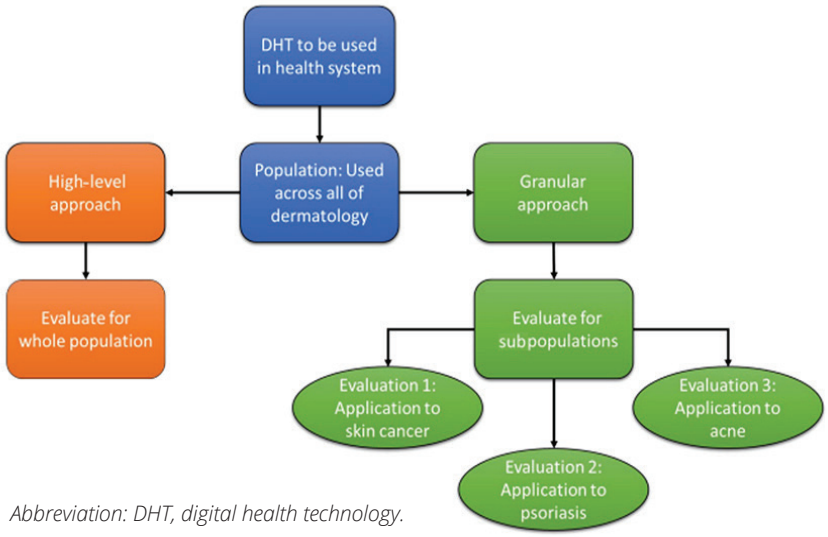
Lessons Learned

Regardless of the purpose of the DHT, the choice of comparator will be a function of how the intervention interacts with nondigital healthcare.[3] For example, the DHT may complement or substitute other types of healthcare delivery or administration systems. In settings where the intervention is implemented in an area where a DHT is already used, the relevant comparator may be simpler to identify, unless the new DHT has a wider aspect that the current DHT does not cover.[2]

Discussions with the experts highlighted a key issue linking the population and comparator: whether the DHT distorts the population in the care pathway. For example, if a DHT increases access to a care pathway, then it may result in more people using the pathway, which could change the underlying population (such as by disease severity or age). In some cases, changing the population may also change what is considered "standard care," especially if the severity of the population changes. In some cases, the DHT may only be adjunct to standard care, meaning that the care pathway has not changed. Hence, it is important that any economic evaluation can incorporate and reflect differences in characteristics.[4] Clinical advice should be sought when designing any evaluation plan to understand the possible "spillovers" that may happen with the DHT.

The discussions also identified 2 approaches to conceptualizing economic evaluations of DHTs where the scoped population was less specific. An example of these 2 approaches that looks at a DHT for use in dermatology is visually displayed in **Figure 1**. The first approach is to narrow the population in the evaluation to a specific indication, omitting some of the DHT's potential benefit (a granular approach). The second is to keep the population as broadly defined as possible, but to simplify the health economic evaluation to key costs, resource use, and health outcomes that are generalizable across a range of conditions and pathways (pragmatic approach). This approach may lead to omitting potential benefits through simplifying the decision problem. The appropriate choice is likely to be decided on a case-by-case basis for each specific DHT, depending on the variation and generalizability of the care pathway. **Table 1** provides a

Figure 1. Evaluation of DHTs with wide populations.



Abbreviation: DHT, digital health technology.

Table 1. Comparison across interventions.

	Pharmaceuticals	Medical devices	Digital health technologies	Implications of differences for modeling
Population	This is often defined by the therapeutic indication (licensed if available). Population size calculated using national or local sources.	The people using the device or having it used on them. Population size calculated using national or local sources. May also differ due to the nature of the intervention, but this issue is more common to DHTs. For example, home testing/ sampling when compared with clinic or GP testing.	The people using the technology or having it used on them. Population size calculated using national or local sources. May differ due to the nature of the intervention. Access and behavior change are the 2 key drivers of changes in population.	If the population changes with the implementation of the digital health technology, the underlying prevalence, severity of disease, or other characteristics could impact the effectiveness of the intervention.
Comparators	All relevant comparators that would be used for the same indication.	All relevant comparators.	All relevant comparators.	Implications and difficulties for selecting the correct comparator, depending on the value proposition, changes to the care pathway, regional differences in care, and isolating the impact of some DHTs being adjunctive to standard care.

Abbreviations: DHT, digital health technology; GP, general practitioner; NICE, National Institute for Health and Care Excellence.

summary of the different populations and comparators used in different interventions. This table shows how broad the comparator can be for DHTs compared with other interventions, as well as how varied the population can be that the DHT is used on.

Key Evaluation Considerations for Now and the Future

Important considerations for DHT evaluation are listed in **Figure 2**. DHTs may be used on a wide-ranging population, rather than being defined by the therapeutic indication as is usually the case with pharmaceuticals. Population subgroups, where the effectiveness of the DHT may be expected to differ, must also be taken into consideration. Furthermore, DHTs may also subvert care pathways, meaning that the population and underlying prevalence may be different for DHTs with respect to the comparator, particularly where the DHT changes the patient access within a care pathway. Understanding how the population may vary needs to be taken into consideration when evaluating a DHT.

Identifying the relevant comparator can be a difficulty in evaluating DHTs. Comparators may differ at local, regional, and national levels, particularly where a DHT is replacing part or all of a face-to-face care pathway.

Future considerations could include the development of a centralized body for DHT evaluation. In England, this could be divided between NHS England and the Department of Health and Social Care (DHSC). Other countries may also wish to appoint a centralized body and team dedicated to these evaluations. Each DHT should have a measured scoping approach to determine the appropriate balance between granularity and pragmatism to inform decision makers.

Figure 2. Key considerations for DHT evaluation.

Abbreviation: DHT, digital health technology.

Summary

DHTs may need much more localized, flexible models and a detailed scoping of the population and comparators than other healthcare interventions. To identify the full benefit of a DHT, evidence generation should look to capture broader populations where possible. Decision makers should be supported to develop a framework to identify and discuss the risk, generalizability, and unquantifiable benefit of adopting DHTs with wider populations. Future research should consider how distorting populations within care pathways from implementing DHTs could impact study design and data collection in order to determine the true effectiveness of DHTs.

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A Global Approach to Tackling Alzheimer's

Interview With Paola Barbarino, CEO, Alzheimer's Disease International

Q&A

Paola Barbarino, CEO of Alzheimer's Disease International, shares her insights into the growing global challenge of the disease and the urgent need for action across all income settings. In this interview, she discusses the importance of postdiagnosis support, the burden on caregivers, the impact of stigma, and the role of governments in creating Alzheimer's-inclusive societies. Barbarino also calls for a unified, collaborative approach to tackling the disease worldwide.

"When Alzheimer's Disease International approached me to lead the organization, I thought this was incredibly important, not only because I had not previously worked in healthcare, but also because I was genuinely curious to learn more about the field."

– Paola Barbarino

PharmaBoardroom: You started your career in education and the arts before moving into the field of Alzheimer's advocacy. What led you to this transition and what fuels your passion for dementia awareness and policy change?
Paola Barbarino: I have explored various fields because I have always been interested in many areas, particularly working in the international space. When Alzheimer's Disease International (ADI) approached me to lead the organization, I thought this was incredibly important, not only because I had not previously worked in healthcare, but also because I was genuinely curious to learn more about the field. My interest was further intensified by personal experiences with Alzheimer's and dementia affecting friends and family members. I recognized this as an extraordinary opportunity to join a significant nonprofit at a very interesting time. Since joining, I have grown increasingly passionate in the space because ADI serves as the global voice for people who are among the least privileged and face the toughest circumstances. When I speak at global meetings, I always remember that I am representing individuals who cannot speak up for themselves. This responsibility fuels my commitment. I believe the group we represent is one of the last frontiers in exclusion. Many still dismiss older age, and I have observed ageism at every level of society. We are facing a massive issue with the global aging population while most governments worldwide continue to ignore the problem.

PB: What you see today as the biggest gaps when it comes to addressing Alzheimer's?
Barbarino: I refer to our 2024 World Alzheimer's Report on Global changes in attitudes to dementia, which revealed that 65% of healthcare professionals believe that dementia is a normal part of aging. This statistic demonstrates that many people around the world still do not understand the true challenges posed by Alzheimer's and dementia. New treatments and diagnostics are emerging, and hope is on the horizon for the patients and families affected. However, widespread

misconceptions about the disease persist, presenting a major challenge in our current healthcare ecosystem.

When it comes to allocating the proper resources to this area, I have participated in many discussions about cost-benefit analyses. I fully understand the necessity of these assessments as a taxpayer, but I find it difficult to grasp why governments can make such decisions for certain disease areas but seem reluctant to invest in Alzheimer's disease. Often, it appears that decision makers believe that older individuals are less deserving of investment, which is not acceptable. This issue is compounded by the fact that ageism is present not only among the general public, but also among healthcare professionals. I recall a report from the Organisation for Economic Co-operation and Development that noted over the course of a doctor's training, only 12 hours are dedicated to education on dementia and Alzheimer's. This is a serious concern because these professionals are responsible for making decisions about cost benefits, medicine prescriptions, and the implementation of diagnostics. Addressing these educational gaps is essential for improving outcomes in Alzheimer's care.

PB: What are the key barriers to the early detection of Alzheimer's? In your perception, how equipped are healthcare professionals to recognize and diagnose the disease?
Barbarino: I have mentioned that 65% of primary care doctors consider Alzheimer's or dementia as an inevitable consequence of aging. And yet, in our 2024 report, we found that 90% of the general public would seek a diagnosis if a disease-modifying treatment were available. This situation is much like the chicken and egg dilemma because every part of the system is interconnected. We cannot address one aspect in isolation—the entire framework needs to move forward together.

Many healthcare stakeholders view Alzheimer's as a giant cruise ship that cannot be easily redirected, but meaningful change requires a comprehensive approach. We must elevate Alzheimer's and dementia as a policy priority, improve risk assessment and prevention, enhance early diagnosis, and raise general awareness. In addition, treatment, care, support, and end-of-life palliative care all need to be addressed simultaneously. The current healthcare systems were not designed for these challenges and must be fundamentally changed to accommodate the evolving needs of an aging population. Even when a diagnosis is made and treatment options are limited, there are many steps that can be taken to improve a person's quality of life.

PB: How critical is the role of screening programs and education initiatives in improving Alzheimer's diagnosis rates?
Barbarino: Recently, I attended a screening program in England designed for older people. The program focused on measuring blood pressure, discussing hypertension, and addressing nutritional habits. However, when I asked whether they would assess cognitive health or perform any brain health evaluation, I was told that it was not on their list of procedures. This was shocking to me, especially in a country that prides itself on comprehensive healthcare.

In our 2022 World Alzheimer's Report: Journey Through the Diagnosis of Dementia, we recommended that people receive assessments at specific age milestones so that doctors may monitor any cognitive decline over 5 to 10 years. Such regular screenings would greatly simplify a timely diagnosis. Unfortunately, even in high-income countries like England, these cognitive assessments are not part of routine practice.

> Only 12 hours are dedicated to education on dementia and Alzheimer's. This is a serious concern because these professionals are responsible for making decisions about cost benefits, medicine prescriptions, and the implementation of diagnostics.

In general, it is rare to see public health campaigns focused solely on Alzheimer's and dementia; usually, they cover multiple health conditions. As a result, specific initiatives to promote brain health and education remain uncommon although they are deeply needed.

PB: Are there any countries in particular that are leading in the implementation of Alzheimer's and dementia initiatives? What can ADI and other countries learn from such examples?
Barbarino: I have recently returned from Malta, where the government proudly informed me that they now have respite care programs available for everyone on the island. Although Malta is a small economy with fewer people living with dementia, it is a significant achievement for them to invest in comprehensive respite care, which is critical.

In my home country of Italy, caregivers did not receive government support until about 3 years ago, when, despite having had a strategy in place, the government only started financing the program. This example shows that even advanced economies may still be catching up. In China, a dementia plan was introduced around 3 or 4 years ago, and they are gradually addressing the challenges of a rapidly aging population.

I believe the most advanced example is South Korea. South Korea launched an all-encompassing initiative, often described as a "war on dementia." They invested significant resources to create a dedicated institute, provided wearables to at-risk citizens, and offered pre-emptive care classes. This comprehensive approach demonstrated that a government-led strategy can have a massive impact. However, even well-established plans are at risk when government priorities and funding change. That is why having a solid plan is crucial—it enables the next government to build on an established baseline rather than having progress evaporate.

Japan's Orange Plan is another excellent example that has been in place for many years and is a model of consistency. On the other hand, some European countries have experienced challenges. For instance, France once had an effective dementia plan, but it was later merged into a broader neurodegenerative

strategy that did not work as well. Italy, despite having a good plan, did not allocate sufficient funding and is only now catching up. But it is particularly concerning to see large, developed countries like Spain without a national dementia strategy.

In South America, some nations have made significant strides by enacting laws that protect the rights of their citizens, and by addressing dementia from a human rights perspective. Although these advances create supportive communities for older citizens, they remain vulnerable to political instability and fluctuations in government support.

> We must elevate Alzheimer's and dementia as a policy priority, improve risk assessment and prevention, enhance early diagnosis, and raise general awareness.

I have also observed innovative initiatives in countries like Switzerland and Japan. In Switzerland, there is a time bank system where younger individuals provide care for the elderly and earn credits that they can later use when they need care. Similarly, in Japan, a program called Fureai Kippu, known as the caring relationship ticket, was introduced in 1991. In this system, individuals earn time credits by assisting elderly or disabled persons with tasks such as shopping, cleaning, or providing companionship. These credits can then be redeemed to support their own family members in need when the time comes.

These examples demonstrate that while some countries are pioneering comprehensive, well-funded dementia strategies, others still have significant gaps to address. There are valuable lessons to be learned from these diverse approaches, and it is clear that consistent, well-supported initiatives are essential for making a lasting impact on dementia care.

PB: Beyond lack of access to diagnosis and medical treatment, what are the biggest challenges faced by people living with Alzheimer's and their caregivers?
Barbarino: When someone receives a diagnosis of Alzheimer's or another form of dementia, they need access to information and resources that can improve their quality of life, and that of their family. We are not just talking about the 55 million people currently living with dementia; we estimate that between 200 and 250 million people are affected when we include family members and caregivers. That impact comes with economic consequences—including loss of income and broader costs to society.

There are also generational challenges that are often overlooked. In some countries, working adults may leave the care of their parents or grandparents to children because they have to work to support the family. This puts a significant burden on younger generations, who may not be prepared or supported to take on this responsibility. The emotional, physical, and financial toll on families is immense.

One of the biggest challenges is the lack of support for caregivers. Many experience guilt, feeling they are not doing enough, but it is crucial for caregivers to take breaks and look after their own well-being. Respite care is essential. If caregivers are exhausted or unwell, they cannot properly care for their loved ones. Governments must step in to support this need. We are also seeing new challenges, such as the growing vulnerability of older adults to fraud and financial abuse. This can come from external scams or even from within families. Stigma is another major issue. In our 2024 World Alzheimer's Report on stigma, we found that more than 40% of people living with dementia and their caregivers reported withdrawing from social activities after receiving a diagnosis. This isolation is harmful and can accelerate the progression of the condition. It is vital that we help people remain socially engaged and included in their communities.

PB: What opportunities exist for cross-functional collaboration among the diverse stakeholder groups such as governments, HCPs, patients, industry, NGOs, etc. What partnerships or alliances is ADI fostering to drive systemic change in Alzheimer's?
Barbarino: In theory, collaboration is essential and effective. But in practice, it can be challenging to identify who your real stakeholders are and who can be a genuine partner. It is easy to gravitate toward people who do exactly what ADI does—they understand our work, and it feels familiar. However, our role at ADI is to step outside of that comfort zone and engage with people and organizations who may not be directly involved in the Alzheimer's space.

> One of the biggest challenges is the lack of support for caregivers. If caregivers are exhausted or unwell, they cannot properly care for their loved ones.

Over the past 5 years, we have made a concerted effort to do just that—to create more global conversations and reach new audiences. The ministries of health or social welfare already know what is needed, they are professionals. Sometimes, what we need to do is bring them together with caregivers, with people living with Alzheimer's, and with other stakeholders, so they can hear directly how urgent the situation is. Too often, Alzheimer's and dementia are things that governments feel they can "come back to later," but it cannot be postponed. It is a public health emergency, and governments know that action is required.

The key to making a real impact in Alzheimer's care is that everyone must feel they have a stake in the solution. Only then can we create the kind of systemic change that is truly needed.

PB: How must healthcare systems evolve to better accommodate the needs of Alzheimer's patients?
Barbarino: In 2020, the number of people aged 60 and over surpassed the number of children under 5. That shift alone should tell us something about the urgency of preparing our healthcare systems for an aging population.

From a healthcare system perspective, government bodies are

often underfunded and unprepared to support changes as new diagnostics and treatments for Alzheimer's become available. This is what concerns me. We have these innovations coming into the space with new diagnostic tools and new treatments, but many governments are simply not preparing for them. Are there enough neurologists and psychiatrists? Are there enough diagnostic facilities, infusion centers, and MRI and PET scanners? Have countries considered colocating infusion services with cancer centers to optimize resources? Generally, I am not seeing that level of planning, although a few countries are making progress towards these benchmarks. But this is no longer just about preparing for the future. These treatments are already here, and if action is not taken, healthcare systems will fail the very people we are meant to support.

> Healthcare systems and governments must move faster, plan better, and work more collaboratively with the other health stakeholders. Only by doing that will we be able to serve Alzheimer's patients properly.

We must also talk about the pace of policy change. It is simply too slow. I want to stress this clearly: governments are moving far too slowly. One example is the approval timeline for a recent Alzheimer's medication in Europe took 26 months. Moreover, this treatment is only effective within a specific window after diagnosis. During that approval delay, countless individuals likely passed that window and are now no longer eligible for treatment by the time it gained approval. This is not just a slow process, there are real, human consequences behind each moment that passes.

Healthcare systems and governments must move faster, plan better, and work more collaboratively with the other health stakeholders. Only by doing that will we be able to serve Alzheimer's patients properly.

PB: What gives you the greatest optimism, and where do you feel the greatest cause for concern with regard for the future of the Alzheimer's field?
Barbarino: What gives me the greatest optimism is the progress we are seeing in research and development. Last year, we conducted a forecast and found that there are over 100 potential treatments currently in advanced stages of clinical trials. These are not just early stage assets, but potential therapies that are well into the later stages of clinical development. That gives me enormous hope.

Of course, there is still a lot to be done in other areas like awareness and care, but I believe that when people see there is real potential for treatment, they will be more likely to take an interest in this field. Often, people turn away from issues they feel powerless to change. But when there is something to be done, something that can make a true difference, I hope the public will begin to demand more action from their governments.

That said, I have not yet seen public demand emerge at the level that I believe we need. There is hope, but we still have a long way to go in raising awareness and pushing for change from a public perspective.

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