JANUARY/FEBRUARY 2025 VOL. 11, NO. 1

VALUE & OUTCOMES SPOTLIGHT

A magazine for the global HEOR community.

THE COST OF **INNOVATION** IN CANCER CARE

FINDING OUR **VALUES** WITH HEOR

ISPOR
Improving healthcare decisions

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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.

ISPOR
Improving healthcare decisions

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Accelerating Access to Cancer Care

Innovation in cancer care, while a beacon of hope for many, contributes significantly to the escalating costs of healthcare globally. Health economics and outcomes research (HEOR) plays a critical role in shaping oncology care for adults by providing evidence on the cost-effectiveness and value of treatments. HEOR data inform decision makers about the economic implications of new treatments compared to existing standards. This evidence aids in reimbursement decisions, optimized resource allocation, and the creation of value-based care models, ensuring that innovative therapies are accessible while maintaining financial sustainability. By assessing outcomes like quality-adjusted life years (QALYs) and treatment costs, HEOR helps to bridge the gap between clinical efficacy and real-world effectiveness, ultimately guiding policy changes and improving overall patient care in oncology.

The feature article in this issue by Beth Fand Incollingo, "The Cost of Innovation in Cancer Care: Finding Our Values With HEOR," examines the financial implications of advances in oncology. It highlights the doubling of global oncology spending from $90 billion in 2016 to $193 billion in 2022, driven by both growing populations and expensive therapies. Rising costs significantly impact patients, evidenced by nearly half of US patients with cancer exhausting their life savings within 2 years of diagnosis. The article explores HEOR as a tool for improving cost-effectiveness and equitable access across healthcare systems. Collaborative global efforts, especially in low-income countries, involve early detection and innovative funding models to optimize cancer care. Challenges include aligning drug prices with health value and ensuring that accelerated drug approvals truly benefit patients.

> Rising costs significantly impact patients, evidenced by nearly half of US patients with cancer exhausting their life savings within 2 years of diagnosis.

Accelerated approvals, designed to expedite the availability of promising therapies, often rely on surrogate outcomes such as response rates rather than long-term endpoints like overall survival. While this can enable faster patient access to potentially life-saving treatments, it raises concerns about the adequacy of surrogate markers in reflecting true clinical benefits. These approvals might lead to increased scrutiny and the need for ongoing postmarketing studies to validate long-term outcomes. Balancing rapid access with robust evidence is crucial to ensure that treatments not only demonstrate efficacious surrogate outcomes but also translate into meaningful survival benefits.

For example, the Joint Clinical Assessment (JCA) framework, advancing in 2025 at the EU level, aims to harmonize oncology drug evaluations across jurisdictions, improving patient access to care. By providing unified clinical assessment reports, the JCA seeks to streamline regulatory processes and reduce the time between drug discovery and patient availability. This could result in more consistent and rapid access to innovative treatments across participating regions, potentially lowering disparities in healthcare delivery. Additionally, harmonized assessments can drive collaborative research efforts and encourage strategic pricing models that reflect collective purchasing power, ultimately enhancing the efficiency of healthcare systems and promoting equitable access to oncology therapies.

Engaging with key stakeholders to accelerate access to innovative therapies requires a strategic, inclusive approach that emphasizes collaboration, communication, and transparency. Stakeholders include policy makers, healthcare providers, patients, regulatory bodies, and pharmaceutical companies. Developing a multichannel

communication strategy, convening stakeholder meetings, and fostering partnerships between public and private sectors can facilitate shared understanding and prioritize patient needs. It is crucial to streamline regulatory pathways without compromising safety to fast-track development and approval processes. Additionally, incorporating patient perspectives early in clinical trials can ensure that therapies align with their needs, potentially improving market access while maintaining focus on equitable healthcare delivery.

> Accelerated approvals, designed to expedite the availability of promising therapies, often rely on surrogate outcomes such as response rates rather than long-term endpoints like overall survival.

The global effort to align cancer care's economic realities with patient outcomes demands the synergy of real-world evidence and HEOR. This involves the understanding and strategic utilization of economic models, policy frameworks, and data-centric approaches to foster a healthcare environment where innovations in oncology can be sustained and equitably accessed. Ultimately, it is not merely about cutting costs but enhancing quality of life and expanding access, ensuring no patient is left behind due to financial constraints.

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

HEOR and the Art of the Possible in Oncology Care

Rob Abbott, CEO & Executive Director, ISPOR

I lost both my parents to cancer. I still remember sitting with my dad in his hospital room, holding his hand as he took his last breath, and helping my mom "die with dignity" at home. Not surprisingly, my interest in the progress of oncology care is both personal and professional. And to be sure, there has been considerable progress in the years since my parents were diagnosed. This is particularly true in the application of health economics and outcomes research (HEOR) to oncology care—the theme of this issue of *Value and Outcomes Spotlight*.

As regular readers of *Value & Outcomes Spotlight* know, HEOR is a multidisciplinary science that is concerned with understanding value in health. In practice, this means closely examining costs and outcomes, as well as factors such as the budget impact of new technologies, patient-reported outcomes, practice patterns, comparative effectiveness, and cost-effectiveness of different healthcare interventions. In view of rapidly rising costs for cancer care, the application of HEOR to oncology becomes increasingly important. As my colleague, Scott Ramsey, MD, PhD, Director of the Hutchinson Institute for Cancer Outcomes Research at Fred Hutch in Seattle puts it: *We cannot make good decisions and improve value for patients until cost and quality are taken into account.*

> At ISPOR, we know there is still much to be done to improve the application of HEOR to oncology care, especially in the domains of data limitations, training for clinicians and health economists interested in collaboration, and the need for prospective economic study of cancer treatment.

There is an underlying concept about value here that I want to emphasize. At ISPOR, when we talk about value, we are intentionally weighing the cost and benefit of various treatments, advocating for the best patient care for the least amount of money. This, in turn, guides us in our ongoing push for evidence-based medicine and cost-containment in healthcare. As ISPOR's CEO, I'm especially excited about the confluence of medicine and economics. Each informs the other in several important ways. As a professional society—and a society that includes many clinicians—we want patients to get access to treatments that work. And if there are treatments that work equally well, we want patients to get the most cost-effective care. Cancer, in particular, is expensive to treat, as I know first-hand, and many treatments offer patients very little in either survival or quality of life. This is where a more deeply embedded commitment to HEOR can help us make smart choices for patients and be wise stewards of limited healthcare dollars.

As the papers collected in this issue make clear, HEOR in oncology care centers on the application of health economics theory and models to cancer prevention and screening, diagnosis, treatment, survivorship, and end-of-life care. HEOR in this context is routinely applied to the study of the organization, production, delivery, and demand for cancer-related care, as well as outcomes such as type, quantity, quality, and cost of care faced by the patient, family, payer, and society. Done well, HEOR can have a substantial and positive impact on how cancer care is delivered and how related healthcare policies are developed and implemented. At ISPOR, we know there is still much to be done to improve the application of HEOR to oncology care, especially in the domains of data limitations, training for clinicians and health economists interested in collaboration, and the need for prospective economic study of cancer treatment. I'm personally interested in and committed to improving the availability of key economic measures in data available to researchers; developing standardized methods to measure the cost of cancer care to healthcare systems and patients; and developing mechanisms to support integration of economic analyses alongside clinical trials. This is by no means an exhaustive list of where growth and development are needed, but progress here might help to paint a picture of what is possible when HEOR is applied to oncology care. And it is here that ISPOR has such potential—ours is a big tent and it needs to get even bigger. We need to welcome researchers from multiple disciplines and enhance opportunities for training in economics and in analytic methods from across the social and clinical sciences. This training is a core competency of ISPOR, and I believe we can draw inspiration from research like that reported in this issue and further build out our training efforts to ensure stakeholders throughout the cancer community feel welcome at ISPOR. This, ultimately, is what our vision of healthcare being accessible, effective, efficient, and affordable is all about.

FROM THE JOURNALS

A Review and Comparative Case Study Analysis of Real-World Evidence in European Regulatory and Health Technology Decision Making for Oncology Medicines

Zong J, Rojubally A, Pan X, et al. *Value Health*. 2025:28(1):31-41

Section Editor: **Agnes Benedict**, Executive Director, Evidera Health Economics & Market Access
Contributor: **Kerry Winter**, Research Associate, Evidera Health Economics & Market Access

Several European bodies have issued guidance regarding the use of real-world evidence (RWE) in regulatory and health technology assessment (HTA) decision-making, reflecting its growing importance in healthcare.[1-5] Zong et al set out to review the use of RWE by the European Medicines Agency (EMA) and major HTA bodies, including the National Institute for Health and Care Excellence (NICE), Gemeinsamer Bundesausschuss (G-BA), and Haute Autorité de Santé (HAS), in their evaluations of oncology medicines to describe trends and compare usage across these institutions.

Zong et al manually retrieved oncology European public assessment reports (EPARs) from the Committee for Medicinal Products for Human Use reviews for oncology medicines with marketing authorizations between January 2020 and December 2022, then conducted single-timepoint searches for NICE, HAS, and G-BA. Noncancer, biosimilar, and terminated assessments were excluded. The authors analyzed trends in RWE usage, types of RWE considered, and acceptance levels across these agencies. They also included case studies on how RWE for specific medicines was evaluated by different HTA bodies.

Table. Case studies of RWE acceptability across EMA and HTA bodies.

Brand name (international nonproprietary name)	EMA	NICE	HAS	G-BA
Abecma (idecabtagene vicleucel)	Supportive evidence as benchmark and RWE follow-up recommendations			Not adequate as formal comparator
Ayvakyt (avapritinib)	Not adequate as formal comparator		Supportive evidence as formal comparator	Not adequate as formal comparator
Lumakras (sotorasib)	Supportive evidence as natural history of disease	Supportive evidence as formal comparator		Not adequate as benchmark
Lunsumio (mosunetuzumab)	Supportive evidence as benchmark and demonstrate unmet needs			Not adequate to understand population indication and unmet need
Piqray (alpelisib)	Follow-up recommendation for safety	Supportive evidence as formal comparator		
Rybrevant (amivantamab)	Supportive evidence as benchmark	Not adequate as a formal comparator		Not adequate as formal comparator
Tepmetko (tepotinib)	Follow-up recommendation for safety	Supportive evidence as a formal comparator		Not adequate as benchmark

Note. Comparative assessment of EMA and HTAs on use and acceptability of RWE for matched oncology medicines.
EMA indicates European Medicines Agency; G-BA, Gemeinsamer Bundesausschuss; HAS, Haute Autorité de Santé; HTA, health technology assessment; NICE, National Institute for Health and Care Excellence.

The findings indicate that RWE is becoming significant in oncology decision making. EMA included RWE in 31% of its oncology assessments, with usage increasing over 3 years. Among HTA bodies, NICE had the highest uptake, referencing RWE in 45% of appraisals, compared to 27.5% for HAS and 24.4% for G-BA. The figure illustrates these differences, with NICE leading in RWE incorporation.

Significant differences were found in how agencies consider and apply RWE. NICE and HAS were more likely to accept RWE as supporting evidence, especially for contextualizing clinical trial results, while G-BA often rejected RWE due to perceived flaws in study design or relevance to the German healthcare context. EMA took a balanced approach, recognizing RWE's value but calling for follow-up studies to address limitations.

The results highlight the potential and challenges of integrating RWE in oncology decision making. The included table, comparing RWE acceptability for specific medicines across EMA and HTA bodies, underscores the variability in assessments. For example, NICE accepted RWE as supportive evidence for Lumykras (sotorasib), while G-BA found it insufficient. These differences

Figure. Extent of RWE included in final approvals and appraisals. Extent of RWE was reported as the percentage of appraisals/approvals including RWE over the total number of appraisals/approvals identified for oncology medicines during the study time periods.

reveal diverse priorities and criteria, emphasizing the need for greater compatibility.

Such inconsistencies may hinder the wider adoption of RWE, undermining its potential to make regulatory and HTA processes more efficient. The study suggests driving consistency in standards to enhance RWE's value for accelerating access to innovative therapies. The EU Joint Clinical Assessment in 2025 presents an opportunity for progress.

A key feature of the study is its structured comparative approach, offering readers a comprehensive overview of RWE usage among major health decision makers in Europe. Comparative case studies covering various cancer areas illustrate how differing agency priorities and methodologies impact RWE acceptability. Limitations include language barriers and potential differences in interpreting agency comments. Future research could explore RWE usage over a longer timeframe or examine how specific methodologies affect decision-making outcomes.

This review and analysis by Zong et al can inform ongoing discussions about RWE's role in regulatory and HTA decision making, highlight progress and areas for improvement, and set goals for advancing RWE use in oncology and beyond.

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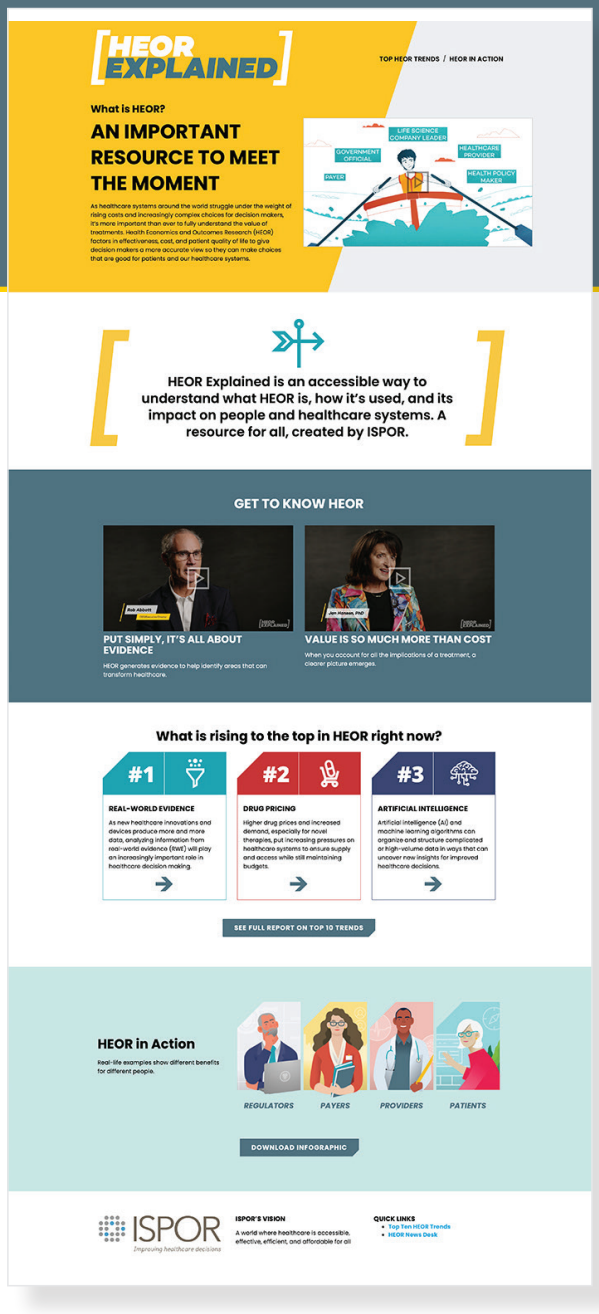
Demystifying the Science Behind Healthcare Decision Making



[HEOR EXPLAINED]

In today's complex healthcare landscape, health economics and outcomes research (HEOR) is emerging as a game-changer. HEOR guides decision makers toward effective, accessible, and efficient healthcare by focusing on patient quality of life, treatment costs, and the overall value of medical interventions.

However, implementing HEOR isn't without challenges. Recognizing the need for more accessible and practical information, ISPOR has launched a groundbreaking "HEOR Explained" website, demystifying this complex field for key stakeholders in the decision-making process, including payers, regulators, providers, and patients.

One key area ISPOR highlights is the power of real-world evidence in healthcare innovations. By analyzing how treatments perform outside clinical trials, HEOR provides a more comprehensive picture of their effectiveness and value.

HEOR, as ISPOR explains, is crucial for guiding decision makers towards effective, accessible, and efficient healthcare. It focuses on patient quality of life, treatment costs, and the overall value of medical interventions. Through its new website, ISPOR is tackling the challenge of making these complex concepts understandable to a broader audience, ultimately contributing to a more patient-centric and sustainable healthcare system worldwide.

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March 26-27 | 10:00AM – 12:00PM EDT

Introduction to Best Practices for Country Adaptations of Economic Models

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- The importance of country adaptations at various stages of each pharmaceutical product's life cycle.
- How to identify key country-specific factors that influence health economic evaluations (eg, healthcare systems, epidemiological profiles, clinical practices, cost structures, modeling requirements, and regulatory frameworks) and trigger model customization across countries.
- Methods for how to select the appropriate data sources for country adaptations to capture accurate and relevant information for use in model adaptation.

April 9-10 | 10:00AM – 12:00PM EDT

Introduction to Modeling

What you will learn in this introductory level course:

- Techniques to discuss the concept and application of decision-analytic models in outcomes research, benefit-harm assessment, economic evaluation, and the efficiency-equity tradeoff.
- The concepts of variability, uncertainty, causality and how to effectively interpret probabilistic sensitivity analysis.
- Which decision-analytic models should be used in economic evaluation and which model type may be suitable for a specific research question (eg, decision tree, Markov model, state-transition microsimulation, discrete-event simulation, dynamic transmission model).

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ISPOR Education

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- Understand how PICOTS-ComTeC can be used with other international and national frameworks and guidelines for DHI assessment and reporting.
- Acquire proficiency in applying PICOTS-ComTeC from examples provided for a range of DHI applications.

March 18 | 11:00AM – 12:00PM EDT

Impact of Delayed Patient Access to Cancer Treatment

By participating in this webinar, attendees will...

- Understand why access to novel cancer treatments is delayed with consideration of the differences between countries and regions.
- Learn how the impact of delayed access to novel cancer treatment can be measured.
- Review the opportunities to address the delayed access to novel cancer treatments and the dramatic implications for patients.

March 25 | 12:00PM – 1:00PM EDT

Challenges in Defining Elements of Value in Duchenne Muscular Dystrophy (DMD) for Decision Making

By participating in this webinar, attendees will...

- Be introduced to the current challenges with traditional value assessment frameworks, with a focus on rare diseases and DMD; and understand the factors influencing societal willingness and ability to pay for treatments.
- Understand the relevance of caregiver burden and why it should be considered an element of decision making for the assessment of new DMD treatments, from a patient and payer perspective including impact on costs and well-being.
- Gain clarity on the potential methods for capturing these factors in the HTA context for DMD, including impact on caregiver costs and well-being.

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- **Artificial Intelligence Enabling Whole Health: Opportunities and Challenges for HEOR and HTA**

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FROM THE REGIONS

The Economic Logic and Reform Direction of Healthcare

Editor's Note: Gordon G. Liu, PhD, Peking University's Boya Distinguished Professor of Economics at the National School of Development and Dean of the Institute for Global Health and Development, is a leading figure in health economics in China. In one of a series of interviews with Chinese economists conducted by NetEase Finance Think Tank, Liu offered his analysis and recommendations for China's healthcare reforms. The following is an excerpted translation of his interview.

The full text in Mandarin is available on the official WeChat blog of the Peking University Institute for Global Health and Development. The interview video can also be accessed online or at the school website https://www.ghd.pku.edu.cn/.

How to Allocate Healthcare Resources

Allocation of healthcare resources is a critical focus of healthcare economics. Whether to prioritize government administrative measures or market price mechanisms in resource allocation is a highly complex issue, and it remains a central point of discussion and debate among health economists. Although both the invisible hands of the market and government intervention are necessary and indispensable, each has its advantages in different areas.

For example, China's current basic universal medical insurance is a government-led institutional arrangement. But if healthcare were to rely solely on individual purchases of commercial medical insurance based on personal need without administrative measures, achieving universal coverage would be much more challenging. Moreover, this approach would lead to strong selection bias, making health insurance unsustainable. Young and healthy individuals who face lower disease risks are less likely to buy insurance, while older individuals and those with chronic conditions are more inclined to do so. This phenomenon, known as adverse selection, would drive health insurance providers to respond in 2 ways. They may raise premiums across the board, leading to fewer healthy policy holders and toward a "death spiral" until the system collapses. Alternatively, they could charge prohibitively high premiums for high-risk groups, a practice that undermines the principle of risk-sharing in health insurance, is politically unfeasible, and would fail to address the burden of disease in modern society.

> To achieve universal health insurance, the government should use its administrative authority through laws and regulations requiring individuals or employers to join the system uniformly, which can largely prevent adverse selection.

To achieve universal health insurance, the government should use its administrative authority through laws and regulations requiring individuals or employers to join the system uniformly, which can largely prevent adverse selection. Therefore, the government can be more effective in pooling the funds for universal health insurance.

However, raising funds for universal health insurance is one thing, and allocating those funds is another. In the case of the former, the government has clear advantages; for the latter, market competition may be more effective. This has led to a discussion in China regarding 2 major models of healthcare fund allocation.

One model involves directly allocating health insurance funds to medical service institutions, known as subsidizing the supply side. This approach primarily relies on administrative measures to distribute funds to healthcare providers before the public pays for services, aiming to offer subsidized or "free" medical services to the public. Lacking direct supervision and market competition provided by consumer choices, the model of subsidizing the supply side would require extremely high administrative planning and execution capacity. Additionally, it may also rely on the professional ethics and moral standards of service institutions and their medical staff, which would be a very difficult task. In short, like other noncompetitive industries, the biggest challenge facing this model would be the high risk of the tragedy of the commons, leading to inefficiency, corruption, and waste.

The second model involves directing medical insurance funds to patients, with the advantage of group buying, known as the subsidizing the demand side model. This model collects medical insurance funds into a shared pool for the public, creating a strong platform to purchase medical services on behalf of the enrollees. This model offers several advantages, including enhancing collective group buying and negotiation power, sharing disease risks and burdens, and amplifying consumer influence by empowering patients to decide where and when to seek medical treatment. Patients make choices and adjustments based on their medical experiences and outcomes, which fosters patient-centered market competition among healthcare providers.

Before China's medical services reform in 2009, there was significant debate over whether to adopt the subsidizing supply-side model or the subsidizing demand-side model for the country's basic medical security scheme. The decision ultimately favored the demand-side model, leading to the current national policy covering more than 95% of the population.

Recommendations for Healthcare Reform in China
China's healthcare reform is a vast and systematic project, characterized by continuous improvements. Two aspects merit further exploration.

Under the UHI framework, medical services are primarily funded through third-party health insurance premiums. This system involves the responsibilities, rights, and interests of 3 key stakeholders: patients, medical suppliers, and payers. Therefore, payment reform should focus on aligning the incentives of these parties to ensure mutual benefit through more efficient payment methods.

Different countries employ a variety of continually evolving health insurance payment methods, from basic fee-for-service to pay-per-visit, diagnosis-related group, capitation, hospital global budgets, pay-for-performance, and various bundled payments like China's diagnosis-intervention package. Each of these methods seeks to balance the responsibilities, rights, and interests of the stakeholders. However, no "best" model has been found that fully satisfies all parties, and such a model may never be found.

The fundamental reason lies in the incentive compatibility problem described in economics. Despite their unique features, these various models share one commonality: Payments are based on illness. The demand side (patients) does not want to be ill but desires generous health insurance; the supply side (providers) prefers more patients and generous health insurance payments; the insurance side (payers) wants fewer patients and lower charges from providers. Given this disease-medicine-insurance relationship with conflicting goals and interests, how can there ever be an incentive-compatible payment solution for all 3 parties?

Could there be an alternative model? With comprehensive universal health records and fully interconnected information systems, combined with analysis by digital technology and artificial intelligence, it may be possible to create individualized health passports. These passports would include essential information that determines personal health, such as biological data, behavioral patterns, socioeconomic status, and medical service records.

Adjusting for the risks shown in health passports, health insurance could allocate an annual routine budget for each individual, based on an overall budget, with exceptional cases (such as accidental injuries) handled separately. Individuals would then sign contracts with healthcare providers based on their personal preferences, with customized health insurance payments. These risk-adjusted payments would be guided by health-based key performance indicators, as graded by the information in individual health passports.

Compared to the disease-medicine-insurance service model, health passports form a health-medicine-insurance model, with the latter paying for health, which can promote incentive compatibility among the 3 parties. Individuals (demand side) want to be healthy, while medical service providers (supply side) and insurers (payers) also want people to be healthy because as long as people are healthy, all parties benefit.

In this way, healthcare institutions would have greater motivation to engage proactively in health promotion activities, such as public education, exercise, diet, behavior modification, and disease prevention. They would also be incentivized to systematically reduce unnecessary healthcare because all parties would share the benefits of improved health and cost savings. As former Harvard president Larry Summers once noted, if medical providers can be paid based on how healthy their patients are, they would have enormous incentives to do all the right things.

Besides the role of medical and health services, personal behavior and lifestyle have a more decisive impact on health. Therefore, the Healthy China 2030 issued in 2016 explicitly emphasizes that individuals should be primarily accountable for their own health. Of course, translating policy documents into individual actions is a challenging task. In this regard, it may be beneficial to explore insights from behavioral economics.

With comprehensive universal health records and fully interconnected information systems, combined with analysis by digital technology and artificial intelligence, it may be possible to create individualized health passports.

Behavioral economics argues that the mainstream economic assumption of the "economic man" is too rigid, as people's behavior is not always rational. This provides a rationale and possibility for appropriate behavioral interventions. Behavioral economics aims to find a more appropriate relationship between laissez-faire behavior and coercive paternalism, thereby providing a "nudge" to individuals. Individuals maintain their autonomy while achieving more rational outcomes.

For example, to encourage exercise habits, personal health exercise points—adjusted for the previously mentioned health passport information—could be redeemed for discounts on goods and services. Additionally, to promote healthy eating, dining expenses could qualify for health-specific discounts at checkout, and businesses offering these discounts could be exempt from related taxes. Furthermore, national health insurance could leverage big data analysis to explore ways to link proactive health behaviors with discounts on insurance premiums and benefits, thereby promoting proactive health behaviors among the populace.

How to Address an Aging Population
The aging population is a global trend that reflects both increased human longevity and declining fertility rates. Despite the challenges it poses, it should largely be seen as a sign of human civilization's progress. In China, the aging transition occurred rapidly, driven by factors like globalization, high economic growth, urbanization, and enhanced social security systems, with the retirement and healthcare systems playing particularly significant roles.

The 1951 Labour Law of the People's Republic of China set the retirement age at 50 for women and 60 for men, which was significantly higher than the average life expectancy of 43 years

at that time. However, by 2023, China's average life expectancy had risen to 77 years. Given this increase, the policy should be updated to align retirement policies with current realities.

In modern society, the gap between biological aging and functional aging is widening, with functional aging often occurring much later. Unlike previous generations, where individuals were considered "old" after 60, many of today's 60-year-olds are still robust and active.

If people were forced to retire based solely on their biological age and collectively exit the labor market at a certain time, it would result in a significant waste of human capital and labor productivity. Additionally, this approach would directly reduce pension fund income while simultaneously increasing pension expenditures. Moreover, early retirement is detrimental to the physical and mental health of the elderly. Research both domestically and internationally indicates that forced early retirement increases the risk of chronic diseases and mortality among retirees, with men being particularly affected. Of course, retirement has its benefits as well. For instance, the retired can enjoy pursuing their interests and engaging in activities they wanted to do earlier in life but couldn't. These advantages are undeniable.

In modern society, the gap between biological aging and functional aging is widening, with functional aging often occurring much later. Unlike previous generations, where individuals were considered "old" after 60, many of today's 60-year-olds are still robust and active.

In many developed countries, the retirement age is often used as a "minimum age" requirement for receiving pensions. For example, in the United States, retiring before the minimum age of 65 usually significantly reduces pension benefits. In China, with its large population and diverse individual physical conditions, preferences, and family situations, some people may wish to retire on time, while others may want to continue working. In this context, a flexible retirement system might be an option. The age for receiving legal pensions can remain unchanged, but individuals may have the freedom to decide whether to retire on time or continue working. From many perspectives, a flexible retirement system is worth exploring.

Regarding the healthcare system, we can divide China's healthcare services into 2 categories: therapeutic services and care services. While therapeutic services are usually provided by large hospital systems, care services can be better offered by community-based primary care facilities with greater accessibility and cost-effectiveness. For the elderly population, medical services and care services are complementary and closely intertwined. As the body inevitably declines with age, timely and adequate care and health maintenance can reduce or even prevent the need for hospital-based therapeutic services. Conversely, without proper care services, the demand for therapeutic interventions increases, leading to avoidable or premature treatments that can harm the patient's physical and mental health and place an additional burden on families and society.

Developed countries have led the way in addressing the challenges of an aging population, creating numerous actionable models and practices worth emulating. For instance, these countries actively promote "de-institutionalization" by establishing out-of-hospital service platforms and enhancing the functionality of community healthcare. This approach provides more suitable working and living conditions for residents in elder communities while significantly advancing the development of community-based, accessible, and affordable long-term care services.

How to Promote Patented Drugs

Pharmaceutical innovation is the main theme of the 21st century. Across different industries, investment in pharmaceutical innovation almost always leads, whether in terms of absolute scale or growth rate. How can China guide, promote, and support pharmaceutical innovation to provide sustainable advancements in human medicine?

A comprehensive understanding of patents is essential for pharmaceutical innovation. Patents play a crucial role because technological innovation in the pharmaceutical sector is characterized by significant uncertainty, substantial investments, long development timelines, and high risks.

In the United States, it takes an average of more than 10 years and an investment of more than $2 billion for a new drug to progress from basic research to successful market entry. Research and development duration for patented drugs in China is similar to that in the United States, around 120 months, but with an average investment of about $200 million. Additionally, in terms of the staged investment structure, China focuses more on posttrial investment, while the United States invests more in pretrial basic research.

Given the high investment and significant uncertainty involved in new drug development, drugs that successfully reach market entry require patent protection to ensure a reasonable return on investment. This provides the incentive and economic foundation for continued pharmaceutical research.

How to Balance New Drug Pricing and Government Procurement

Patent holders have the freedom to set prices, while health insurance purchasers can negotiate those prices. This dynamic is natural and consistent with market principles. Value is created not only through production but also through market exchange. As long as both parties are free to participate, the market exchange generates value and benefits both sides; otherwise, the exchange should not take place.

In drug price negotiations, the bargaining mechanism and rules should be as mutually voluntary and equal as possible to ensure that both the supply and demand sides benefit, fostering sustainable market development. These negotiations should consider both the value in use of the patented drug—its

effectiveness and impact on health—and its value in exchange, reflecting its scarcity in the market.

Let me provide a case study about health insurance negotiations.
In 2019, China introduced nusinersen injection, a groundbreaking drug for treating spinal muscular atrophy (SMA). First approved in the United States in December 2016, SPINRAZA (nusinersen) is the world's first targeted therapy for SMA, a genetic disorder primarily affecting children, leaving them unable to stand and their development delayed or halted.

Nusinersen is administered via injection, with an original market price of approximately 700,000 RMB ($97,674) per injection. The first year of treatment requires 6 injections, totaling 4.2 million RMB ($586,044). Subsequently, patients need 2 to 3 injections annually for life. In late 2021, through negotiations, nusinersen was successfully included in China's national insurance drug list, reducing the cost per injection to 33,000 RMB ($4,605). This negotiation sparked various opinions; critics primarily point out the potential adverse impact this reduction might have on pharmaceutical innovation.

The price reduction from 700,000 RMB to 33,000 RMB was not an arbitrary decision by the health insurance system, though; rather, it was the outcome of a systematic expert evaluation and negotiation process. Since China's national health insurance drug list began its annual updates and adjustments in 2018, a mechanism involving 3 expert groups has been formally introduced to evaluate candidate drugs systematically.

First, the Clinical Expert Group is responsible for evaluating drugs based on clinical experience, with its judgment principle based on clinical necessity for unmet demand. Second, the Fund Calculation Group assesses whether the health insurance budget can afford the inclusion of new drugs without excessively impacting payments for other essential drugs. Third, the Pharmacoeconomics Group evaluates the potential clinical benefits and costs of new drugs, comparing them to existing drugs for the same indications, based on objective data and empirical research. In essence, the groups focus on whether the drug is clinically necessary, affordable, and worth the cost, respectively. To ensure independence, objectivity, and fairness, the work locations and schedules of the 3 expert groups are arranged to avoid overlap.

Pharmacoeconomic evaluations align with World Health Organization (WHO) guidelines: a new drug is recommended if the incremental cost of extending a patient's quality-adjusted life year (QALY) does not exceed 3 times the country's per capita GDP. Countries may modify this threshold based on country-specific factors like per capita income, disease prevalence, and the disease's characteristics at different stages of development.

> In drug price negotiations, the bargaining mechanism and rules should be as mutually voluntary and equal as possible to ensure that both the supply and demand sides benefit, fostering sustainable market development.

For China's current health insurance system, on average it sets one times GDP per capita to pay for one QALY gain for most drugs included in the insurance list. In the case of nusinersen, the negotiated payment ended up being much higher than the average for other drugs, suggesting that the Pharmacoeconomics Group's recommendations considered the added value of nusinersen for its innovation and treatment for SMA as a rare childhood disease.

Having said that, from a pharmacoeconomic evaluation perspective, China's evaluation and negotiation mechanisms still have much room for improvement. For instance, patented drugs that have been on the market for a short time and have limited usage may not fully demonstrate their comprehensive value in the short-term, potentially leading to undervaluation. Furthermore, the market value of any item should encompass both its value in use and value in exchange, the latter reflecting the item's scarcity. Without real-world market exchanges, it is indeed difficult for third-party evaluations to fully account for this. On the other hand, as new drugs undergo real-world use, negative issues related to efficacy, side effects, and other complications may also become more visible, which can potentially lower the market expectations and willingness to pay.

HEOR NEWS

1 Development and Validation of Artificial Intelligence Models for Early Detection of Postoperative Infections (PERISCOPE): A Multicenter Study Using Electronic Health Record Data

(The Lancet Regional Health Europe)

Researchers aimed to develop locally valid models as part of the PERISCOPE AI system to enable early detection, safer discharge, and more timely treatment of patients with postoperative infections, and found the system can accurately predict overall postoperative infections within 7 and 30 days postsurgery. Read more

2 The Potential of Generative Pre-trained Transformer 4 (GPT-4) to Analyze Medical Notes in Three Different Languages: A Retrospective Model-Evaluation Study

(The Lancet Digital Health)

Researchers aimed to assess the ability of GPT-4 to answer predefined questions after reading medical notes in 3 languages. They found that the tool can accurately extract information from these notes and has the potential to transform narrative text into structured knowledge compared with traditional natural-language processing, which generally does not capture the complexity of co-occurring medical problems or disease trajectory over time. Read more

3 Institute for Clinical and Economic Review Publishes Fourth Annual Assessment of Barriers to Fair Access Within US Commercial Insurance Prescription Drug Coverage (ICER)

Partnering with IQVIA, ICER found that major payer coverage policies for the 11 drugs detailed in the report often met fair access criteria for several categories, but said improvements need to be made in the transparency of coverage policy information for consumers and in detailing out-of-pocket costs for patients. Read more

4 Dapagliflozin for the Treatment of Heart Failure With Reduced Ejection Fraction in Brazil: A Cost-Effectiveness Analysis

(The Lancet Regional Health Americas)

A study aiming to estimate the incremental cost-effectiveness ratio of add-on dapagliflozin treatment for HFrEF from the Brazilian public healthcare system perspective found that the addition of the therapy in treating 1000 HFrEF patients yielded an expected value of 366.99 additional QALYs at an incremental cost of $1,517,878.49, resulting in an ICER of $4136.08 per QALY gained. Read more

5 HERA Signs Joint Procurement Framework Contract for COVID-19 Treatment (HERA)

The European Commission's Health Emergency Preparedness and Response Authority (HERA) signed a joint procurement framework contract with Gilead for the supply of the antiviral Veklury (remdesivir). The third agreement, following one that expired in January 2024, includes 13 European Union/European Economic Area countries and allows the purchase of up to 2.25 million vials. Read more

6 Institute for Clinical and Economic Review Publishes Final Evidence Report on Treatment for Epstein-Barr Virus Positive Post-transplant Lymphoproliferative Disease (ICER)

The independent assessment organization found that Pierre-Fabre's tabelecleucel demonstrated superior net health benefits compared with usual care, and could achieve common thresholds for cost-effectiveness if priced between $143,900 and $273,700 per treatment cycle. Read more

7 Unveiling Immunity Gaps and Determining a Suitable Age for a Third Dose of the Measles-Containing Vaccine: A Strategic Approach to Accelerating Measles Elimination

(The Lancet Regional Health Southeast Asia)

As immunity gaps in adolescents and young adults pose an obstacle to measles elimination, this study highlighted a significant gap in young adults aged 20 to 26 years, with researchers theorizing that a booster at the age of 18 to 20 years could potentially close the gap and aid measles elimination programs. Read more

8 Developing Evidence-Based Health Policy for Dementia Care

(JAMA Forum)

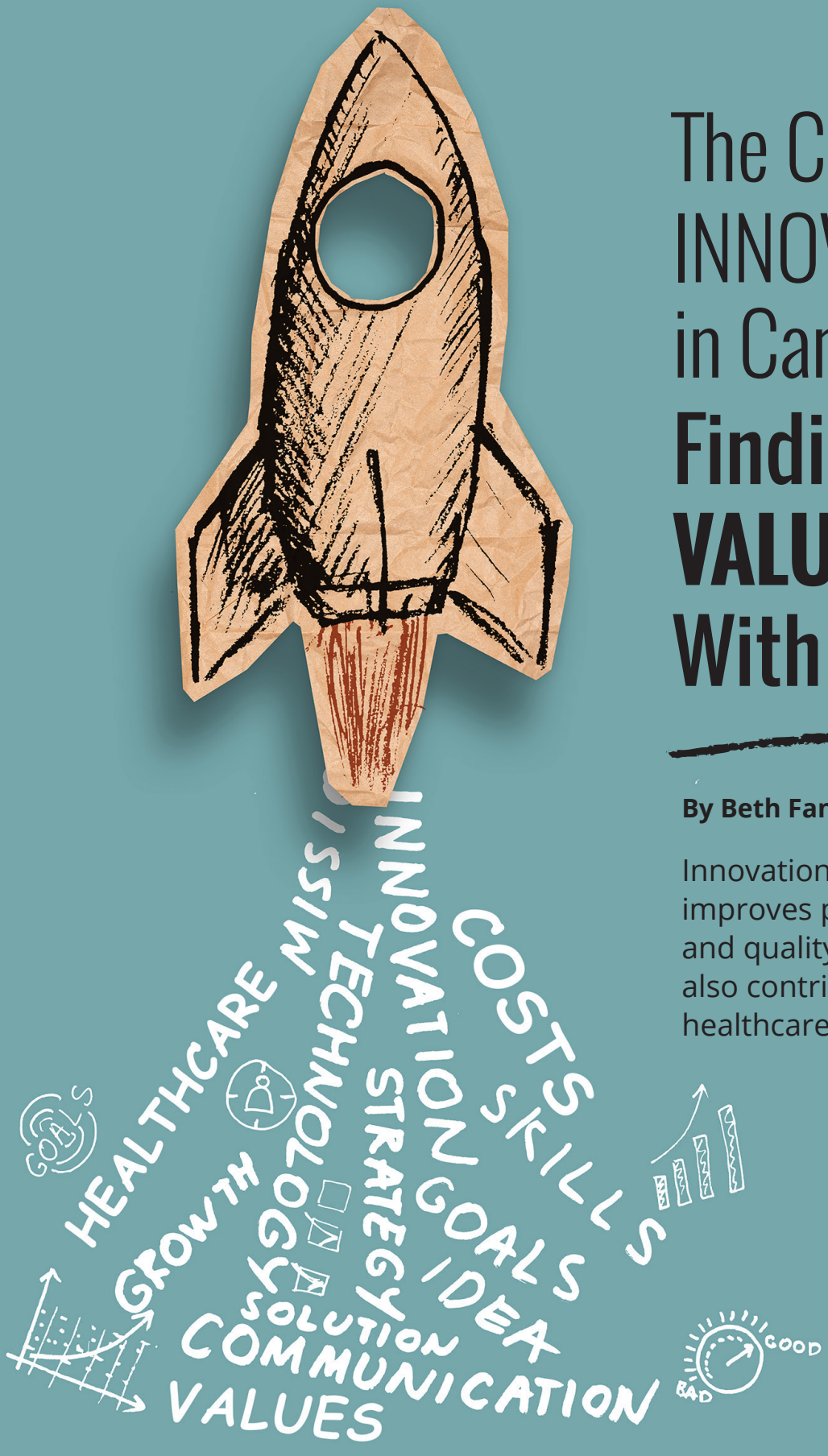
By 2050, the annual cost of care for patients with Alzheimer's disease and related dementias is projected to reach $1.5 trillion in the United States, with 75% covered by Medicaid and Medicare. "Collaboration between health and behavioral economists and clinical experts is needed to bring evidence to bear in informing care delivery and payment policy for the public health insurance programs through which most dementia care will be covered," the authors say. Read more

9 Cost Evaluation of Acute Ischemic Stroke in Latin America: A Multicentric Study (The Lancet Regional Health Americas)

In a study measuring the real costs associated with acute ischemic stroke care in Latin America using time-driven activity-based costing, researchers found significant disparities in stroke costs across healthcare services in Latin America, influenced by variations in treatment accessibility, patient outcomes, and clinical risk profiles, with the primary driver of cost being the length of hospital stay. Read more

10 A Common EU Approach to Data Transparency in Medicine Regulation (EMA)

EMA and HMA (Heads of Medicines Agencies) have published a comprehensive overhaul of their guidance on the identification of commercially confidential information and personal data in marketing authorization applications for human medicines. Officials say the update reaffirms the commitment of regulatory authorities across the European Economic Area to extensive transparency when disclosing information, both in response to access-to-documents requests and in the proactive publication of data once a medicine is authorized. Read more



The Cost of INNOVATION in Cancer Care: Finding Our VALUES With HEOR

By Beth Fand Incollingo

Innovation in cancer care improves patients' longevity and quality of life, but it also contributes to rising healthcare costs.

A glance at oncology spending during a recent 6-year period provides a clear sense of that trend, which is also driven by the needs of a growing and aging global population coupled with fragmented access to cancer care. In 2016, worldwide spending for oncology—converted into US dollars—totaled $90 billion. By 2022, that number had more than doubled to $193 billion.[1]

While the vast majority of oncology dollars go to medical services,[2] significant expenses also crop up at the drug store, where over-the-counter and prescription medications used in cancer treatment are the most lucrative category for pharmaceutical companies.[3]

In the United States and in low- and middle-income countries, those costs not only affect the national bottom line but the economic well-being of patients and their families, whose financial strain or even ruin can threaten their getting the care they need.

> "The closer we can get a manufacturer's announced list price to align with our assessment of a therapy's value, the better off all stakeholders will be."
>
> – Dan Ollendorf, PhD, MPH

A study conducted in the United States between 1998 and 2014 showed that 42.4% of patients surveyed 2 years after a cancer diagnosis reported having spent their life savings on treatment.[4] On average, patients spent more than $92,000. That's a dangerous trend, as patients who declare bankruptcy due to the costs of cancer care have an 80% higher chance of dying than those who are not financially drained.[5]

"As large financial burdens have been found to adversely affect access to care and outcomes among cancer patients, the active development of approaches to mitigate these effects among already vulnerable groups remains of key importance," the research team for the life savings study concluded.

Emerging solutions lie in health economics and outcomes research (HEOR), a field that—through evidence from economic models, clinical trials, and real-world studies—identifies interventions that can help patients receive the most cost-effective care. But how can we make sure that the benefits of HEOR reach adults with cancer across healthcare delivery systems in low- to high-income countries, informing decision making from the preventive stage through cancer screening, diagnosis, treatment, survivorship, and end of life?

It's a complex undertaking that can only succeed through collaboration between governments, health technology assessment (HTA) experts, pharmaceutical and medical device companies, academia, healthcare systems, doctors, payers, patients, and advocates.

Weighing the Value of Cancer Drugs

In high-income countries that offer universal healthcare, the billion-dollar question is how to work within a fixed budget to choose the interventions that deserve coverage—including targeted oral drugs distributed at pharmacies, chemotherapies or immunotherapies administered in clinical settings, medical devices, imaging technologies, diagnostic and screening tests, and innovations in the way services are delivered.

In England, that exercise leads to positive recommendations for about 80% of proposed interventions, while separate assessments make room in the budget by identifying approved strategies that are no longer cost-effective, said Meindert Boysen, PharmD, an independent HTA expert and former Director of Health Technology Evaluation and Deputy CEO of the National Institute for Health and Care Excellence (NICE).

When advising the UK's National Health Service about the value of cancer interventions, he said, NICE considers not only health economics and relative clinical effectiveness but also insights from stakeholders, so that decisions incorporate "equity and social justice." Thus, the organization may deem a drug with weaker evidence cost-effective if it's likely to fill an unmet need for a small population of very sick patients without causing large-scale displacement of other promising technologies.

Still, NICE's decisions can be controversial, as was its 2024 recommendation against Enhertu (trastuzumab deruxtecan), a treatment for metastatic HER2-low breast cancer that has been approved in 13 countries, and for which about 1000 patients in the United Kingdom would have been eligible.[6] Patient advocacy group Breast Cancer NOW said the decision marked a "dark day" in the United Kingdom.

There are different challenges in America, where the US Food and Drug Administration (FDA) evaluates interventions without considering prices, which are set later by pharmaceutical companies and paid for by patients and their private or public insurers.

That strategy does little to hold down the cost of treatment, which may explain why the United States lags behind Australia, Canada, and the United Kingdom in health gains per dollar spent.[7,8] In 2020, median per capita spending on cancer care in the United States was $584, the highest among 22 high-income countries.[9] Yet, America's cancer mortality rate was just below the median within that group, with 6 countries reporting more favorable outcomes.[10]

Working to rein in the costs of American cancer care is the Institute for Clinical and Economic Review (ICER), an independent, nonprofit organization that measures the value of proposed interventions compared with existing alternatives and suggests fair prices.

This small organization reviews just 12% to 15% of the drugs approved by the FDA each year, and pharmaceutical companies don't have to comply with its suggestions. Still, Chief Scientific Officer and Director of HTA Methods and Engagement Dan Ollendorf, PhD, MPH, believes ICER's work has the potential to shave dollars off the cost of cancer care.

"Patients in the United States, especially those who are privately insured, feel the impact of high list prices in their coinsurance and copayments," Ollendorf said. "The closer we can get a manufacturer's announced list price to align with our assessment of a therapy's value, the better off all stakeholders will be."

Through an 8- or 9-month evaluation process that involves multiple stakeholders, ICER suggests launch prices for drugs that are nearing regulatory approval. It also spotlights nonevidence-based price hikes made by pharmaceutical companies, like those that resulted in combined additional spending of $276 million in 2023 for targeted cancer drugs Darzalex (daratumumab, indicated for multiple myeloma) and Cabometyx (cabozantinib, indicated for advanced renal cell carcinoma, hepatocellular carcinoma, and differentiated thyroid cancer).[11]

There are signs that ICER's efforts are having an effect. An estimated 59% of US payers include ICER data in their formulary decisions,[7] and recent research suggests that therapy prices tend to be lower at launch if an ICER assessment is released before the manufacturer announces a price.[12]

Establishing Value Thresholds

With an array of healthcare systems come divergent methods for evaluating the cost-effectiveness of cancer treatments.

ICER assesses the value of interventions according to a threshold of $100,000 to $150,000 per quality-adjusted life year (QALY) or equal-value life year (EVLY) gained. NICE also employs the QALY, but with a lower threshold of $28,471 to $42,857 per unit, which can lead to different decisions about value.[7]

A study that compared what the 2 organizations decided about 11 cancer drugs found that they agreed on the cost-effectiveness of 7 of the medications.[7]

"Most new cancer drugs were not cost-effective in either the United States…or England," the authors wrote. "Furthermore, NICE's capacity to negotiate price discounts and access schemes result(s) in much lower cost per QALY valuations and more favorable recommendations than those of ICER for similarly assessed cancer drugs."

While the QALY is a popular way to measure net health gain, there are alternative formulas designed to better incorporate quality of life and avoid bias, including the ISPOR value flower.[13] Still, striving for equity is a common goal no matter which algorithm is used.

To keep a level playing field for people with other conditions, ICER doesn't inflate its value threshold when assessing oncology interventions. Ollendorf is convinced that doesn't harm patients with cancer, though, as ICER still finds some of the highest prices in oncology care to be justified—as it did for Kymriah (tisagenlecleucel), a single-dose CAR-T cell immunotherapy whose introductory price was $475,000.[14,15]

"If a CAR-T drug turns a fatal blood cancer into a survivable one, you're adding a lot more years of life," he said.

NICE uses different rationales, Boysen said, relying on 3 thresholds for value depending on disease severity.

"They're calculated on the basis of what you might otherwise experience as a healthy person and what you're losing because of where you are in your cancer care," he said. "Then there's a fourth, even higher threshold for ultra-rare genetic diseases that are generally not cancer."

> "Neither clinical nor HEOR data are static phenomena. This is a dynamic and evolving evidence base that needs to be tracked, and with artificial intelligence, we may get even better at doing that."
>
> – Meindert Boysen, PharmD

While The Netherlands factors in the lost productivity of patients who can no longer work due to their cancer, the United Kingdom does not, Boysen added, as that "might value younger people who are producing over and above people who are older and mostly consuming."

Grappling With Insufficient Evidence

A key obstacle for healthcare decision makers is that oncology treatments often receive accelerated approvals based on single-arm studies.

"Without knowing their impact on progression-free or overall survival," Ollendorf said, "there's a lot of uncertainty about the benefits these interventions are bringing."

In the United States, that often leads to insurers paying for therapies that turn out not to be beneficial. According to an analysis by Harvard University researchers, only 43% of the cancer drugs that gain accelerated FDA approval eventually demonstrate a benefit on overall survival or quality of life.[16]

ICER does an informal 1-year checkup on interventions it's reviewed, inviting manufacturers to supply additional information about effectiveness. And the FDA can rescind

a therapy's approval or indication based on the results of confirmatory trials. But according to Ollendorf, it's not unusual for the agency to keep a treatment on the market if it meets other metrics, such as improving quality of life or helping to fill an unmet medical need.

"The United States has more cancer drugs on the market than most other high-income countries," Ollendorf said, "because regulators elsewhere may have taken a more conservative view of the evidence."

> "From the moment something suspicious is found through self-examination or screening, patients need to be in a system where their path to diagnosis is clear and undisrupted."
>
> – Mimi Choon-Quinones, PhD

In response to the rise in accelerated submissions, NICE has revamped its Cancer Drugs Fund, helping create a route for the conditional approval of oncology treatments that don't meet usual standards for cost-effectiveness.[17] The fund collects real-world evidence about these drugs following their approval—typically for around 2 years, although this is not a strict limit—to assess whether they should remain in use.

"Countries like The Netherlands, Italy, and France have also looked extensively at collecting real-world evidence after accelerated approvals," Boysen said. "They recognize that neither clinical nor HEOR data are static phenomena. This is a dynamic and evolving evidence base that needs to be tracked, and with artificial intelligence, we may get even better at doing that."

Applying HEOR Principles in Low-Income Countries

Experts in high-income countries often bring HEOR-related initiatives and other medical interventions to their neighbors in low- or middle-income countries as a means of helping people affected by cancer while supporting a stable world economy. Mimi Choon-Quinones, an attorney and healthcare researcher, orchestrates those strategies in Africa.

As founder and board chair of Partners for Patients, an all-volunteer nongovernmental organization, Choon-Quinones has coauthored the Pan-African Parliament's healthcare legislation, policies, and model laws and cocreated the continent's 55-country framework to strengthen its healthcare systems.

Her efforts have hatched a range of pilot programs, from a pediatric vaccinology initiative that cures most cases of Burkitt lymphoma to a course that teaches hungry patients to grow food so they'll be strong enough to endure cancer treatment.

Eventually, Choon-Quinones expects those initiatives to make excellent HEOR use cases, as they demonstrate high value for a low investment.

Her work has highlighted the cost-effectiveness of catching cancers early, before advanced treatment is needed, a concept that rings true worldwide.

"What we've learned through all of our research, roundtables, ad boards, interviews, and surveys on the continent is that what costs the system the most money is a lack of timely diagnosis," said Choon-Quinones, who is also a senior vice president with the International Myeloma Foundation. "From the moment something suspicious is found through self-examination or screening, patients need to be in a system where their path to diagnosis is clear and undisrupted."

Breast cancer is the second-leading cause of oncologic mortality in Ghana and is especially problematic there because women are the country's primary earners, Choon-Quinones said. That's why Partners for Patients is opening 6 early detection cancer research centers in Ghana, and pharmaceutical companies are signing memoranda of understanding with the country's government to support diagnostic services, referrals, and discounted breast cancer treatments.[18]

> "Rather than waiting for companies to come up with new technologies, maybe we should specify the kind of solution we need for a disease like breast cancer and then ask them to start investigating."
>
> – Meindert Boysen, PharmD

Partners for Patients has also built capacity in Ghana by training medical staff throughout the military to conduct and support oncology clinical trials, Choon-Quinones said. The organization runs a "mini medical school" that brings in physicians from high-income countries to foster medical upskilling and enhance scientific knowledge.

The Future of HEOR in Cancer Care

Looking ahead, HTA experts hope to see the introduction of interactive economic models of treatment paradigms for specific cancers, similar to the IQVIA Core Diabetes Model.[19] ICER recently developed a platform of its own, the subscription-based ICER Analytics, which contains nearly 60 economic models that users can customize to reflect their experience. Choon-Quinones believes such engines could save global healthcare systems billions of dollars.

The experts are also enthusiastic about other emerging tactics, including the following:

- Increased and earlier efforts to incorporate patient goals and values into decision making about cancer interventions.
- Joint scientific advice, a strategy that enables pharmaceutical companies to seek guidance from HTA firms and regulators about the design of their phase III trials, with the goal of generating more patient-relevant outcomes.
- New payment strategies that could help healthcare systems handle costs for expensive treatments like CAR-T therapy through the better management of money and risk over time.
- Finally, the HEOR leaders suggested some changes to the way cancer care is studied and delivered.

"Rather than waiting for companies to come up with new technologies, maybe we should specify the kind of solution we need for a disease like breast cancer and then ask them to start investigating," Boysen said.

Choon-Quinones added that instituting universal healthcare should be prioritized.

"When patients are healthy and you invest in them, national economies exponentially grow," she said. "The countries that say they have universal healthcare should take down the facade and go deeper. And the countries that don't have it should recognize that it's a great place to start, because it ultimately saves a lot of people."

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By the Numbers: Oncology Care

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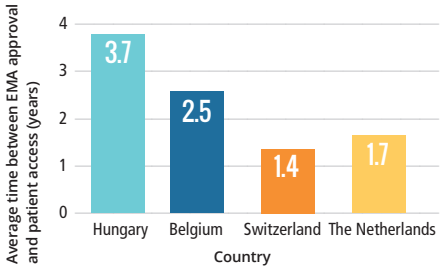
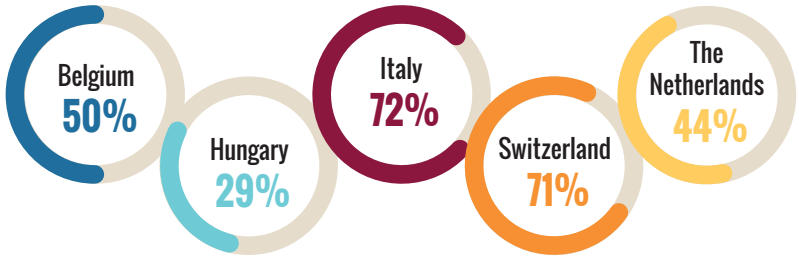
Patient Access to Innovative Oncology Medicines in Europe

Average time to first patient access to new treatments in hospital



First access to selected oncology medicines*

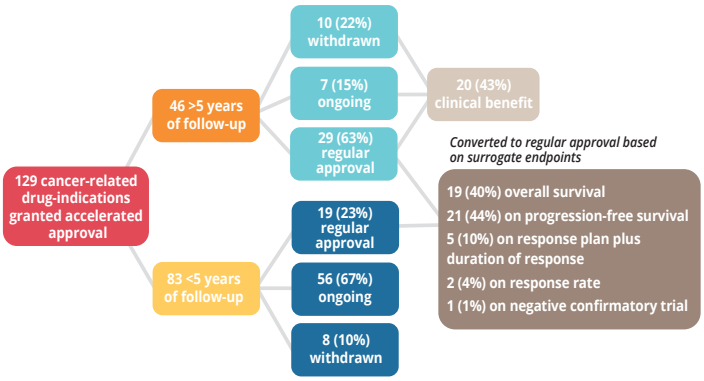


*Off-label use or early access program.

Recommendations for Health Economics Research in Cancer Treatment

- Improve availability of key **economic measures.**
- Create **comprehensive datasets** that include patients from all payers.
- Increase availability of **real-time data.**
- Creation of **health economics–focused symposia** within major cancer treatment society meetings.
- Provide a mechanism to support **integration of economic analyses data collection** alongside clinical trials of cancer treatment.
- Develop transparent and **standardized measurement methods** of the cost of care.
- Develop standard **methods to estimate the economic burden of treatment** on patients in terms of time, out-of-pocket costs, and productivity.

FDA Accelerated Cancer Drug Approvals: Do They Ultimately Demonstrate Clinical Benefit?



How COVID-19 Has Affected Cancer Screening Programs

Canada 3-month interruption in breast cancer screening →7% drop in cancer diagnosis

6-month interruption in breast cancer screening →14% drop in cancer diagnosis

USA Screenings for breast, colon, prostate, and lung cancers were reduced by 85%, 75%, 74%, and 56%, respectively.

Taiwan The total number of newly diagnosed cancers fell by 22.2% during the lockdown period.

Italy Cancers were diagnosed in 50% of patients during 2018 and 2019 compared to 39% in 2020.

Real-World Evidence of Colonoscopy Screening for Colorectal Cancer Based on a Stepwise Approach

Chisato Hamashima MD, PhD, Teikyo University, Tokyo, Japan, on behalf of the Evidence Review Committee for the Japanese Guidelines for Colorectal Cancer Screening

A stepwise approach serves as an alternative evaluation method when randomized controlled trials do not evaluate the efficacy/effectiveness of new techniques.

This approach is an evaluation method combined with the test accuracy of new techniques and performance for cancer screening programs.

The effectiveness of the screening program can be predicted using a stepwise approach, as demonstrated in real-world settings.

Background

Colorectal cancer (CRC) poses a significant health burden in developed countries, prompting widespread screening efforts. There are several options for CRC screening, which are as follows: guaiac fecal occult blood test (gFOBT), fecal immunochemical test (FIT), stool DNA test, flexible sigmoidoscopy (FS), colonoscopy, and CT colonography. Although early adoption of new techniques has been expected, CRC mortality reduction should be evaluated before introducing new screening methods into public health programs. However, the evidence obtained from randomized controlled trials (RCTs) is limited to gFOBT and FS, and it requires long-term follow-up. Fecal testing has been used commonly for CRC screening worldwide, and the main method has changed from gFOBT to FIT. The World Endoscopic Organization (WEO) developed a stepwise approach to evaluate a new technique, predicting final results based on test accuracy and program performance in CRC screening.[1] This framework was adopted to evaluate FIT, and RCTs have not been evaluated.

What is a stepwise approach?

A stepwise approach is an alternative evaluation method when the efficacy/effectiveness of new techniques is not evaluated. Pepe et al originally proposed the basic concept of a stepwise evaluation of cancer screening, which moves from development of a new technique to its adoption in screening programs.[2] Based on this concept, the WEO stepwise approach is divided into 4 phases for assessing a new technique for CRC screening (**Table 1**).[1] A comparator should be defined as a standard screening method for evaluating efficacy. In Phases 1 and 2, the new technique's test accuracy is compared with the standard screening method. For a new technique to be adopted for the screening program, at least equal sensitivity and specificity are required. The program performance results reflect the effectiveness of the new technique, which evaluates mortality reduction by RCTs. In phase 3, program performance is assessed in one round of the screening program and through multiple rounds in phase 4.

> Although early adoption of new techniques has been expected, CRC mortality reduction should be evaluated before introducing new screening methods into public health programs.

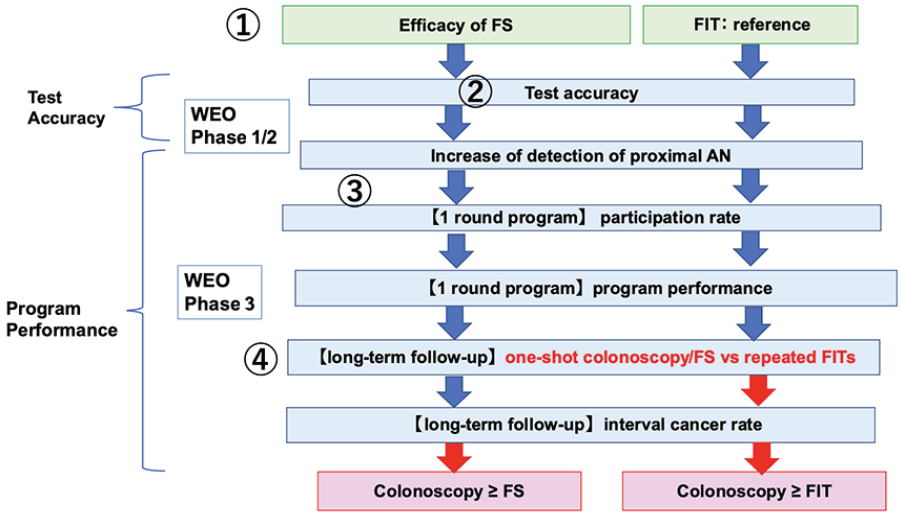
Methods of a stepwise approach

We evaluated the effectiveness of colonoscopy screening following a stepwise approach, modifying the WEO method (**Figure 1**). In CRC screening,

Table 1. A stepwise approach for evaluation of CRC screening presented by the World Endoscopic organization[1]

Process	Nature	Main aim
Phase 1	Prescreening: Retrospective estimation of ability to discriminate between cancer cases and controls without neoplasia	Test accuracy
Phase 2	Detection of lesions along the neoplastic continuum: prospective clinical studies	Test accuracy
Phase 3	Initial screening evaluation: single round of screening	Program performance
Phase 4	Screening program evaluation over multiple rounds	Program performance

Figure 1. A stepwise approach for evaluation of CRC screening



Abbreviations: AN, advanced neoplasia; CRC, colorectal cancer; FIT, fecal immunochemical testing; FS, flexible sigmoidoscopy; WEO, World Endoscopic Organization.

precancerous lesions are the target outcome as well as invasive cancers, which can be removed by colonoscopy before they progress to invasive cancers. The outcomes of these studies are performance indicators, including the participation rate and advanced neoplasia (AN)/CRC detection rates in the program. To assess the effectiveness, we divided the process into the following main steps: Step 1, the efficacy of FS, a comparator, was confirmed for CRC mortality reduction based on RCTs.

> The results of a stepwise approach could predict a screening program's effectiveness, which is reflected in real-world settings.

FIT has also been adopted as another comparator commonly used for CRC screening. In Step 2, test accuracy was compared between colonoscopy and other screening methods. In Step 3, program performance indicators from a single round of screening were compared. Finally, in Step 4, the long-term follow-up results were compared with other methods after one-shot colonoscopy. The screening interval was usually 10 years for colonoscopy, 5 years for FS, and 2 years for FIT. Even in the same observation period, the frequency differed depending on the screening method.

We defined the inclusion criteria based on population, intervention, comparators, and outcomes (PICO) for selection program performance RCTs. The target of CRC screening is asymptomatic persons. In Step 3, program performance indicators were compared based on single-round RCTs, and a meta-analysis was performed based on intention-to-treat (ITT) and perprotocol (PP) analysis. The result of ITT analysis reflects actual programs that offer population-based screenings.

Evaluation of colonoscopy screening for CRC

Step 1: Based on 15 years of follow-up, 4 RCTs evaluated the efficacy of FS screening for CRC. The pool analysis results suggested a 20% mortality reduction from CRC (relative ratio 0.80, 95% CI: 0.72-0.88).[3]

Step 2: Four studies calculated the sensitivity of colonoscopy compared with CT colonography (CTC). One study reported the sensitivity of FIT, FS, CTC, and colonoscopy performed simultaneously. The sensitivity for AN detection was consistently higher in colonoscopy than in others, even if the adenoma size was changed.[4]

Step 3: Candidate articles were searched for using the MEDLINE, Embase, and Igaku-Cyuo-zasshi (the Japanese library) from inception to February 2021. From over 7000 articles, those that did not meet the inclusion criteria, including duplicates and non-RCTs, were excluded. Finally, 14 RCTs that evaluated the program performance of CRC screening were selected. All studies evaluated program performance in a single-round screening. Ten studies from European countries, 2 from the United States, and 2 from Asian-Pacific countries reported program performance RCTs. In the ITT analysis, the participation rate of the meta-analysis was lower in colonoscopy screening than in FIT and FS (**Table 2**). Although the AN detection rate was higher in colonoscopy screening than in FIT and FS, the CRC detection rate was higher but not statistically different. In the PP analysis, AN and CRC detection rates were higher in colonoscopy than others.

Step 4: Although no RCT existed in multiple-round screening, program performance indicators were compared between one-shot colonoscopy/FS and repeated FITs.[5] This study combined

Table 2. Meta-analysis of program performance of colorectal cancer screening

Analysis	Indicators	Ref*	Colonoscopy RR (95%CI)	Ref*	Colonoscopy RR (95%CI)
ITT	Participation rate	FS	0.83 (0.78-0.88)	FIT	0.49 (0.22-0.89)
	AN detection rate	FS	1.15 (0.88-1.51)	FIT	2.25 (1.40-3.61)
	CRC detection rate	FS	1.08 (0.49-2.37)	FIT	1.48 (0.66-3.43)
PP	AN detection rate	FS	1.45 (1.00-2.07)	FIT	4.14 (3.03-5.85)
	CRC detection rate	FS	1.30 (0.60-2.85)	FIT	2.57 (1.17-5.87)

Abbreviations: CI, confidence interval; FIT, fecal immunochemical testing; FS, flexible sigmoidoscopy; ITT, intention to treat; PP, per protocol; RR, relative risk.
** Ref=Reference*

the results of 3 randomly selected population-based trials. In the ITT analysis, the AN/CRC detection rate was higher in repeated FIT than in FS and colonoscopy. In the PP analysis, AN detection rates were higher in FS and colonoscopy but CRC detection rates were similar to FIT. On the other hand, the interval cancer rate was lower in colonoscopy than in FS and FIT.

Is it possible to adopt program performance RCTs to evaluate cancer screening?

Even if RCTs have not confirmed efficacy, the program performance can be examined by a head-to-head comparison. When an established method like FS is defined as a comparator, the results of colonoscopy performance could be compared. The success of cancer screening programs depends on the participation rates. The International Agency for Research on Cancer handbook defines participation rates as an essential factor in estimating the effectiveness of cancer screening.[6] When colonoscopy is adopted for cancer screening, adherence is lower, leading to a decreased AN/CRC detection rate. Although high sensitivity was confirmed in the colonoscopy screening, the program performance as a cancer screening was deemed insufficient because of the low adherence rates.

Comparison with the Nordic-European Initiative on Colorectal Cancer study

Colonoscopy is anticipated as a new method for CRC screening, with 5 ongoing RCTs yet to yield conclusive results. The Nordic-European Initiative on Colorectal Cancer (NordICC) study, conducted in Poland, Norway, Sweden, and The Netherlands, is one of the RCTs intended to evaluate CRC mortality reduction by colonoscopy screening. They reported intermediate results based on a 10-year follow-up.[7] In the ITT analysis, mortality reduction from colorectal cancer could not be observed because of the low adherence in the intervention arm (risk ratio 0.90; 95% CI, 0.64-1.16). Although mortality reduction from CRC was observed in the colonoscopy screening arm at the PP analysis, it was no greater than in those of FS. The meta-analysis results for program performance RCTs are similar to the intermediate results of the NordICC study for colonoscopy screening. Some RCTs reported baseline results and lower participation rates in colonoscopy screening. However, the United States and other countries have observed a difference in participation rates in colonoscopy screening.

Lessons learned

The results of a stepwise approach could predict a screening program's effectiveness, which is reflected in real-world settings. It is challenging to validate the impact of CRC mortality reduction by colonoscopy screening, and the balance of benefits and harms cannot be determined. The efficacy is still uncertain until the publication of final results of RCTs, which are expected by the late 2020s. Although some countries have already introduced colonoscopy screening, such as the United States and Poland, most countries will be cautious in introducing it as a public health policy.

The Evidence Review Committee for the Japanese Guidelines for Colorectal Cancer Screening

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Funding

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Understanding and Addressing the "Burden" of Asking Patients to Complete Patient-Reported Outcome Measures in Clinical Trials: A Brief Summary

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PROMs can provide valuable and informative data about how patients feel and function while using treatment in a clinical trial.

Too much burden on the patient and site can reduce the quality and completeness of PROM data.

The concept of burden includes PROM length, clarity and relevance, and time for completion.

Researchers can reduce perceived burden and maximize PROM data quality through generation of a carefully considered PROM strategy and purpose.

Introduction

Patient-reported outcome measures (PROMs) are questionnaires that explore how a patient perceives their medical condition, treatment, and/or trial experiences in a reliable, valid, and interpretable way. PROMs are becoming a critical component in the development and commercialization of new treatments and are now included in most pivotal clinical trials.[1] Sometimes PROMs are the only way to understand the effects of treatments in trials, and to explore how treatment impacts symptom severity/frequency, day-to-day functional impairment, health-related quality of life, and treatment satisfaction. Many trials include multiple PROMs (a PROM battery) to measure different facets of how a patient is feeling or functioning.

The people designing clinical trials must balance the desire for insights with the potential burden on the patient and the research team.[2] PROMs may seem burdensome to trial contributors unfamiliar with their value, so it's important to note that insights from PROMs can be used for multiple purposes: to inform regulatory and payer decision-making, customize clinical care, establish expectations, and inform healthcare initiatives. Their value is thus significant across intervention development, and knowing this encourages researchers to collect as much PROM data as possible. However, if the PROM burden is too high, this will result in respondent fatigue, a lack of engagement, and a high level of missing data/unreliable responses undermining the utility of the data and increasing levels of participants' dissatisfaction.

How many PROMs are too many?

No two PROMs are created equal. A clinical trial PROM battery can range from a few items, administered at occasional site visits, to more than 100 items administered weekly. While the latter seems burdensome, it may not always be. For example, Atkinson and colleagues administered 14 PRO questionnaires comprising 176 to 180 items to high-risk bladder cancer patients undergoing radical cystectomy and urinary diversion.

> Insights from PROMs can be used for multiple purposes: to inform regulatory and payer decision-making, customize clinical care, establish expectations, and inform healthcare initiatives.

Despite the large number of items, patients reported low response burden.[3] There are plenty of other examples of patients willingly completing large PRO batteries in clinical trials.[2] Burden should not, therefore, be defined by simply looking at the number of items in a PROM/battery and people designing clinical trials should not assume that less is better.[4] While it is important to select PROMs that are not unnecessarily long and complex, having a unilateral focus on brevity may lead to missing the measurement of some important factors. It is perhaps relevant therefore to look beyond the number of items/PROMs when trying to define burden.

So, what defines PROM burden in clinical trials?

Multiple factors contribute to perceived PROM burden beyond the number of items/PROMs in a battery. These include difficulties in understanding or completing the PROMs, inadequate time for completion of the PROMs, and perceived irrelevance of the items/PROMs from a patients' perspective.[2-8]

Difficulties in understanding or completing the PROMs

In general, a PROM has a brief set of

instructions (telling the participant what aspect of their life or experience they are being asked about, what amount of time they should think about when answering the PROM [the recall period], etc, and a set of questions with response options. When patients do not understand the PROMs, engagement decreases. This leads to missing data or unreliable responses (eg, patients may choose a random option because they didn't understand the question). A lack of understanding may be caused by unclear instructions or recall periods, and questions that are complex or unclear, therefore making it difficult to choose between answers. Although most modern PROM developers are constructing (and testing) simple questions to minimize confusion, some older PROMs (still widely used) are complex. When a PROM battery is used, different PROMs using varying recall periods, presentations, response scales, and repetitive requests of patients (choose a statement, select a number, cross a line, etc) can cause further confusion.

Inadequate time for completion of the PROMs

Sometimes in clinical trials there is not enough time allocated for patients to complete the PROMs or for staff to administer them. When the PROMs are aligned with a site visit but they don't fit into the site staff's workflow, missing data is common. Frequency of PROM administration is also relevant. Often, researchers reduce the number of timepoints to minimize burden, although the relationship between frequency of PROM collection and completion rates is weak. Rather, it seems that patients are willing to complete PROM data frequently (including multiple times per day) where they perceive it as an opportunity to tell their story and where they perceive a benefit to them personally.

Perceived irrelevance of the items/ PROMs

Patients don't want to answer questions that don't seem relevant to their experiences or to help in understanding their condition or treatment(s). Perceived relevance of PROM items is an important indicator of burden. Indeed, Rolstad and colleagues said "if the questions are deemed relevant, patients are more likely to be motivated to respond" (p. 1107).[4] They also highlighted the importance of avoiding overlapping items. For example, if a battery includes one PROM to measure clinical symptoms and another to measure generic quality of life, they may both have items that evaluate pain and activities of daily living. When studies involve multiple measures covering similar or identical concepts, or repetitive items, greater levels of burden are perceived.

Meaningfulness of PROMs is further reduced when patients do not receive the feedback of trial results after the study has ended.

Other contributors to PROM burden

Characteristics of the population enrolled in a trial should be considered in PROM inclusion. Level of literacy, physical fitness, health status, and technological aptitude and access influence perception of PROM burden. Social norms and cultural perspectives should further be considered when developing PROMs and administering them in diverse populations.

Figure. Causes and remediation for PROM burden in clinical trials

Abbreviation: PROM, patient-reported outcome measures.

How can we decrease PROM burden in clinical trials?

As described, burden in clinical trials is a multifaceted construct. Below we present some strategies that aim to minimize burden. We have intentionally selected solutions that we perceive as "low-hanging fruit"—that is, things that are already being done in some places (albeit not systematically), things that prior research has shown the benefit of, and things that are feasible within regulations of clinical trials. However, we recognize that there are also barriers to implementing these solutions, including trial budget, timeline, and adequate scientific, logistic, and resource considerations.

> Involving patients in the design of a PROM strategy offers an opportunity to identify and address any difficulties in understanding or completing the PROMs through iterative cognitive interviews.

Involve patients in PROM strategy design

Trial participants want to share what they believe to be relevant and want this information to be used in decisions about whether treatment should be approved for use by other people like them.[9,10] Involving patients in the design of a PROM strategy offers an opportunity to identify and address any difficulties in understanding or completing the PROMs through iterative cognitive interviews.[1] These ensure appropriateness, acceptability, and clarity in the instructions, items, and response options, and test whether the proposed recall period is one that is sensical for the PROM concept being measured, and what people can accurately recall.[2,8] Patient-centric design warrants collecting and presenting relevant data to inform decisions about treatment.[2]

Present PROMs in a way that is easy for people to engage with

How PROMs are visually presented can be modified to improve usability and ease of completion.[1] Flexible modalities may also increase ease and convenience[2] and improve inclusivity.

When administering PROMs via an electronic device (ePROMs), there are opportunities to present the study aim and a thank you message that is not easy to do on paper forms. This shows respect and gratitude, and it acknowledges a participant's time commitment. Navigational guides and a progress indicator can also aid in following ePROM flow. Simple layout and consistent formatting help identify instructions and questions, and make it easier to respond. Notifications and reminders prompt participants to complete the required ePROMs at the right time, while using computer-adaptive testing or branching logic ensures only relevant PROMs/questions are displayed, reducing burden.[2]

> Explaining to participants why PROM data are being collected, how it will be used, and informing them of results of the research maximizes engagement and investment by the participants in providing considered data.

Protecting adequate time for completion of the PROMs

Appropriate and dedicated time for patients to complete PROMs is part of study design, set-up, and training. For example, home (instead of site) administration of PROMs, use of a patient's own smartphone (BYOD), or splitting PROMs administration may be considered to increase convenience and reduce time requirements.

Researchers may also need to convince clinic staff of the relevance and importance of PROMs where they have a role in administering them as well as ask them to help identify ways in which PROMs can be administered without interrupting normal workflow.[9]

Help people understand how the data will be used

Explaining to participants why PROM data are being collected, how it will be used, and informing them of results of the research[10] maximizes engagement and investment by the participants in providing considered data.[2,6,9] Recent initiatives aim to train researchers to communicate data to patients in an accessible way. For example, the UK Health Research Authority has launched the "Make it Public" strategy[11] to encourage sharing of trusted information from health and social care research studies in public forums. As part of this, Parkinson's UK developed a "Research Communications Toolkit" to assist researchers in continually communicating with study participants.[12]

Conclusion

A poorly conceived PROM strategy may be considered burdensome for patients and produce unreliable data. A well-conceived PROM strategy, on the other hand, developed in conjunction with patients and with the aforementioned points in mind, is likely to produce valuable and informative data about how patients feel and function while using treatment in a clinical trial. A more detailed overview of techniques to address PROM burden is provided in Aiyegbusi et al.[2]

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Are There Specificities for Assessing Quality of Life and Utilities in Rare Diseases for Economic Evaluation in France: A Case Study of Published CEESP (Health Economic and Public Health Committee) Opinions

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In this review of rare diseases' economics evaluations in France, half of the industrial's submissions were rejected due to utilities estimates, despite that quality of life is an important component of these diseases.

The review's results show no specificity in a rare disease context: HAS guidelines for utility estimations were applicable in most cases.

For the evaluations that were not rejected, the average ICER was €827,000 per QALY, and half of the ICERs were classified as "extremely high."

Background
As part of the responsibility of the French National Authority for Health (HAS) for assessing the cost-effectiveness and budget impact of healthcare products, the Commission for Economic and Public Health Evaluation (CEESP) issues an economic opinion that is sent to the Healthcare Products Pricing Committee (CEPS) to help guide price negotiations.

The economic analysis must follow the principles outlined in HAS's economic evaluation guidance documents to ensure valid information. Based on HAS's technical review of the manufacturer's application, the CEESP may express concerns about the methodology used in the economic evaluation, such as efficacy, safety, utility score, and costs. A reservation is noted if a methodological choice does not comply with current recommendations. The severity of the reservation depends on the argument's acceptability and the impact of the methodological choice on the results, especially regarding uncertainty.

> A recent review of international HTA processes for assessing orphan drugs showed that there are generally no specific processes or requirements for these drugs, rather adjustments to the usual standards.

Reservations are graded based on the product being assessed and the analysis context. For example, noncompliance in a quality-of-life evaluation method is more impactful if health-related quality of life is a significant outcome for the product or disease.

The reservation levels are categorized as follows: Minor reservations do not meet current recommendations but have minimal impact; important reservations, while justifiable, significantly affect findings; and major reservations invalidate the economic evaluation, rendering it unreliable despite any justifications.

Introduction
Measuring quality of life (QoL) in rare diseases can be challenging as in small samples or populations without cognitive ability to answer QoL questionnaires requires a proxy (third person) (including pediatric).[1] These challenges are identified in the French Health Technology Assessment (HTA) guidelines for health economics, but no standards are proposed.[2] A recent review of international HTA processes for assessing orphan drugs showed that there are generally no specific processes or requirements for these drugs, rather adjustments to the usual standards.[3]

Despite the lack of dedicated methodological guidelines and procedures, development of orphan drugs presents specificities and challenges beyond QoL measurements, potentially adding a level of complexity for HTA and decision making.[4]

One of the main challenges is the lack of long-term efficacy data—which is generally accepted for orphan drugs, resulting in the use of surrogate endpoints[5]—especially for mortality, making it harder for the health economic evaluation to conduct a proper cost-effectiveness analysis, incorporating uncertainty around life-years estimates. It raises the need for robust QoL and utility measures to conduct cost-utility analyses that could be used for decision making.

Another specificity of orphan drugs is pricing and economic model for tariffication; addressing small prevalent diseases, research and development (R&D) costs could generally not be borne through large sales, leading to high treatment costs at the patient level. At the HTA level for health economics, it

usually leads to high incremental cost-effectiveness ratios (ICERs).[6] As a result, some countries attempted to adapt their decision-making framework as in the United Kingdom (National Institute for Health and Care Excellence [NICE]) with a dedicated ICER threshold for orphan drugs.[7] However, such decision criteria do not exist in France, where health-economic assessment is only part of the pricing-setting procedure.[a]

This context raises 2 main questions in France:

- How is utility estimated and assessed in health economics for rare disease evaluations?
- How are resulting ICERs appreciated by CEESP in the absence of a specific framework?

Objectives

This study aims to assess the impact of the methodology used to estimate utility values on the conclusions of the CEESP for orphan drugs. This assessment will identify accepted deviations from guidelines for utility estimates in the context of rare diseases, presenting methodological challenges and sparse data.

Additionally, the study analyzes the conclusions of the economic assessment, with a focus on ICER levels, when validated by CEESP. The goal of this study is to identify from past decisions of CEESP if there is a *de facto* framework for economic assessment in the context of rare disease in France.

Methodology

The analysis is based on a review of CEESP opinions in rare disease (orphan drugs), published from 2014 to the end of 2021. A focus was done on QoL measures used by manufacturers and assessments by CEESP, including ICER level.

Relevant information for the research questions were reported in an analytical grid:

- **General and administrative elements:** product, date of assessment, indication, pediatric population or not;
- **Claims of the manufacturer for HTA procedure:** added value claimed (ASMR[b,c]) and obtained from French clinical HTA committee TC (transparency committee), target population, budget impact, technical exchange (written questions and answers) conducted or not during health economic assessment, hearing/observations from manufacturer on draft opinion;
- **Conclusions' synthesis:** maximum grading of methodological reservation[d] and details (number and topic), ICER level, ICER qualification, committee's conclusion, complementary data asked on utility;
- **Economic evaluation's details:** data sources for utility, QoL questionnaire, patients' capacity to answer questionnaires, person answering QoL questionnaire (patient, parent, other caregiver), integration of caregiver QoL, details of reservations on utility assessment.

Descriptive and quantitative analyses were performed to understand type of methodology accepted by CEESP for measuring health utility in rare disease contexts.

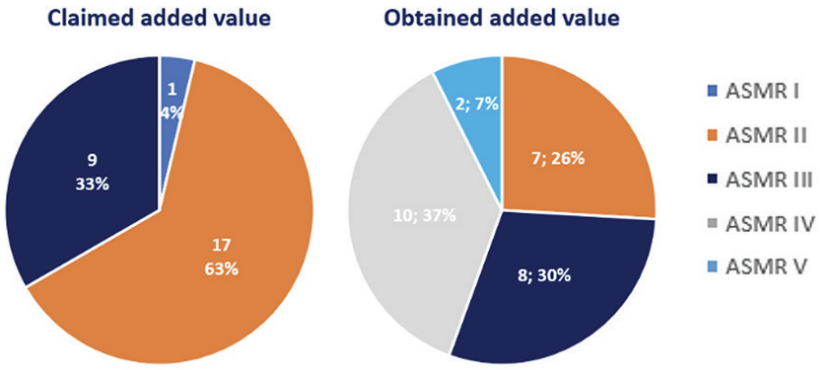
Results

Twenty-seven CEESP opinions on rare diseases were analyzed: the size of the target population varied from 75 to 8830 patients. Fourteen opinions included both pediatric and adult populations and one only pediatric.

Claimed "added value" were mainly important and moderate, but obtained added values were lower (**Figure 1**).

As a comparison, in 2021, for all drugs assessed, excluding rare diseases, TC granted 0.8% major added value,

Figure 1. Claimed vs obtained added value



In the context of the French HTA, "claimed added value" (ASMR revendiquée) represents the anticipated improvement in medical benefit asserted by the manufacturer based on submitted evidence. In contrast, "obtained added value" (ASMR obtenue) reflects the actual level of improvement recognized by HTA committees after thorough evaluation. This distinction underscores the discrepancy between manufacturer claims and the evaluated benefits of new treatments within the French healthcare system.
Abbreviations: ASMR, added value claimed; HTA, Health Technology Assessment.

[a] Health-economic assessment is produced by CEESP (Health Economic and Public Health Committee) and then economic information assessed is used by the decision makers: pricing committee for healthcare products (CEPS), as an input for price negotiations.
[b] In France, ASMR levels (Amélioration du Service Médical Rendu) indicate the degree of improvement a new drug or medical device offers compared to existing treatments, ranging from ASMR I (major improvement) to ASMR V (no improvement). These levels help determine reimbursement and pricing within the healthcare system.
[c] Economic assessment in France concerns only drugs with claimed ASMR ≥ III (Major, level I, important level II, and moderate level III, on a scale up to IV minor and V absence of added value).
[d] Methodological reservations from CEESP are rated from major (invalidation of the analysis), important (strong uncertainty and impact), to minor (deviation justified or low impact expected).

0.8% important, 22.7% moderate, 28.9% minor, and 46.9% inexistent.[8] Proportionally higher "added value" for drugs assessed in this study could be explained by: i) demonstration of the eligibility to health-economic assessment being required for innovative drugs[2]; ii) context of rare diseases, with an important part of drugs claiming a change in care paradigm as few therapeutic options exists.

Across the economic assessments of the 27 drugs studied, 17 (63%) had important methodological reservations over at least one aspect of the economic evaluation, while 10 (37%) had at least one major reservation.

Challenges in utility assessment for orphan drugs

Out of the 27 opinions, only 2 (7%) had no reservation on estimation and implementation of health utility in the economic evaluation, and 52% (n=14) had at least one important reservation, denoting a significant estimated impact on the results of the economic evaluation.[9]

More strikingly, among rejected opinions (n=10), 55% (n=6) were due to inappropriate methods used to measure utilities, noting the importance of adequate QoL assessment (**Figure 2**).

These results show the difficulties in obtaining and implementing robust utility estimates in economic evaluation in the context of rare disease, despite the fact that quality of life is an important component of these diseases.

Methodology rejected: role of data sources

Methodology recommended by HAS[e] **(Guideline 15)**: "The utility scores used to weight life-years should be estimated using a multi-attribute approach, comprising the collection of health state data from patients via a generic questionnaire and the valuation of health states according to the preferences of the general population."[2]

In 80.7% of opinions studied, patients answered their own QoL through the EQ-5D questionnaire, as recommended by HAS. No differences were noted between adult and pediatric populations and no proxy respondent had to be asked when the data came from a clinical trial. Except for 2 opinions, patients had the cognitive capacity to respond directly to QoL questionnaires.

Caregiver utility was not considered in the opinions studied, except for one including it in a sensitivity analysis. Despite being potentially important in a rare disease context (especially for pediatric populations), this could be explained by poor data availability (or quality) even if it enters in the scope of HAS's guidelines.

In one case, a cost-efficacy analysis was proposed in anticipation of methodological difficulties associated with utility estimates.

Repartition of data sources for utility is presented in **Figure 3**. Health utility was informed from literature in most cases, clinical trials, or both.

For 5 opinions with major reservation on utilities (out of 6), CEESP rejected the methodology considering inappropriate data source:

- Vignette study (n=2), rejected because they were not completed by patients themselves
- Expert opinion (n=1), HRQoL was not estimated by patients as well
- Disease-specific questionnaires (n=2)

For the opinions without major reservation, when the methodology was considered appropriate by CEESP, it was supported by robust data sources: literature (n=11), clinical trials (n=7), or both (n=3).

These results show no specificity in the context of rare disease and that the general method recommended by HAS is applicable.

Methodology accepted: challenge of willingness-to-pay for orphan drugs

When the methodology was accepted, CEESP assessed efficiency of the drugs, but issues appeared with higher ICER levels. For 19 opinions (70%) with efficiency conclusions, the average ICER was 827,000 €/QALY (ranges from 70,651 €/QALY to 2,700,000 €/QALY) (**Figure 4**).

In 50% of the cases, CEESP considered these ICER levels to be extremely high and in 2 cases, they were qualified as "exceptionally high" or even "unacceptable."

Figure 2. Maximum methodological reserve level associated with utility

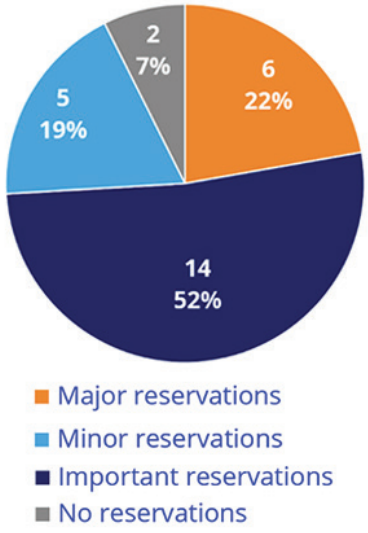
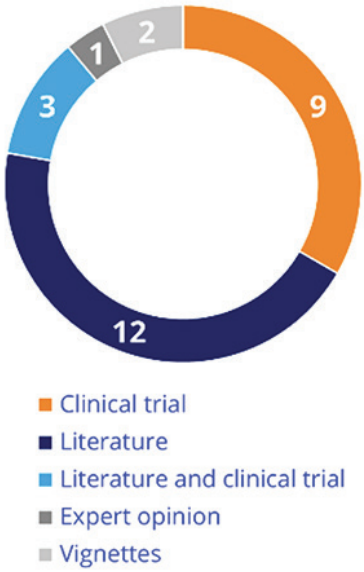


Figure 3. Source of health-related quality of life data

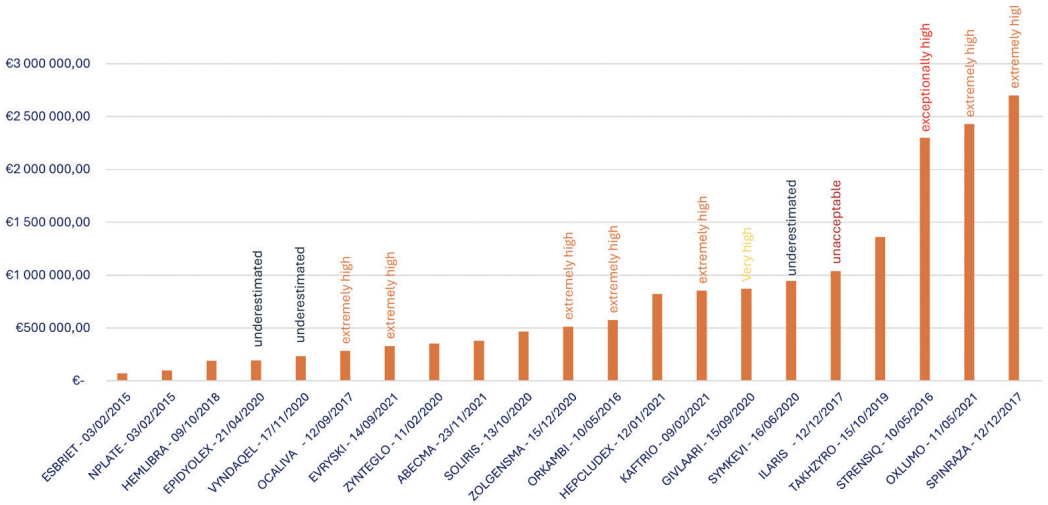


[e] HAS stands for the "Haute Autorité de Santé," which translates to the High Authority of Health. The HAS is an independent public authority in France responsible for assessing health products, treatments, and medical practices to ensure quality, safety, and effectiveness in healthcare.

By way of comparison, the average ICER for all innovative medicines subjected to economic evaluation by the CEESP between 2014 and 2020 was 287,821 €/QALY, and only 25% of ICERs were higher than 239,145 €/QALY.[10]

The ICER levels in rare disease are well above traditional value for money thresholds, emphasizing the specific problem of high-cost orphan drug pricing: how to articulate cost efficiency, affordability, and social value in the assessment of healthcare value.[11]

Figure 4. ICER levels and qualification by CEESP



** Complementary analysis used by the HAS despite a major reservation on the utility*
*** ICER of the subpopulation for which there is no major reservation*
Abbreviations: CEESP, Health Economic and Public Health Committee; HAS, Authority for Health; ICER, incremental cost-effectiveness ratio.

Implications for HTA Practitioners:

- Prioritize the use of EQ-5D data or employ mapping techniques from clinical trials whenever feasible, particularly in the context of orphan drugs where robust QoL data can significantly impact HTA outcomes.
- Consider the utilization of utility values from published literature, including proxies for disease, similar health states or events modeled. Ensure these values are contextually appropriate for rare diseases.
- Encourage the development and adoption of advanced methodologies for capturing QoL impacts in rare disease populations, such as patient-reported outcomes (PROs) tailored to the specific challenges of orphan drug evaluation.

Conclusion

Despite methodological difficulties associated with utility assessment in rare diseases, most of the analyses studied implemented CEESP guidelines without specific issues related to HRQoL measures, demonstrating that CEESP general guidelines can be effectively applied in the context of orphan diseases.

Beyond the methodology, when results can be estimated, they illustrate the debate in academic literature questioning the relevance of higher thresholds for rare diseases. In this context, other criteria may be considered by decision-makers as equity to treatment access, supporting research and development in the field of rare diseases through higher prices, or budget impact considerations.

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Health Economic Modeling in Obesity: Does the Structure Matter?

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This research offers guidance on how a specific structural modeling approach might influence the clinical and health economic model outcomes in the context of obesity.

The structure of a health economic obesity model matters if clinical events are to be predicted most accurately.

If the purpose of the model is primarily the incremental health economic comparison, the structure does not matter that much, as incremental results are fairly comparable.

Background and Introduction

This research presents the lessons learned from a 5-year research project at Maastricht University aiming to increase trust and confidence in selecting and interpreting results related to commonly applied structural approaches used in health economic obesity models.[1]

Obesity is an abnormal or excessive fat accumulation often defined as a body mass index >30 kg/m^2 (BMI).[2] Obesity reached epidemic proportions and is a leading risk for global deaths and morbidities.[3] Worldwide, obesity among adults has more than doubled since 1990. The global age-standardized prevalence of obesity increased from 8.8% in 1990 to 18.5% in 2022 in women and from 4.8% to 14.0% in men.[4]

> Obesity reached epidemic proportions and is a leading risk for global deaths and morbidities.

Accordingly, global healthcare systems are facing populations with increasing prevalences of obesity-associated diseases, such as type 2 diabetes, coronary heart disease, stroke, osteoarthritis, different cancer types, and others. Besides the severe health consequences of these diseases, the World Obesity Federation predicted that the global economic impact of overweight and obesity will reach $4.32 trillion annually by 2035, if prevention and treatment measures do not improve.[5]

To evaluate the impact of such prevention and treatment measures on the chronic obesity-associated diseases and the related burden to patients and healthcare payers, health economic (HE) models are frequently applied. The results of such HE models are centrally triggered by the chronic nature of the obesity-associated diseases that develop over a long time horizon. In a perfect world, long-term clinical studies would be performed to evaluate the impact of obesity prevention and treatment measures on chronic obesity-associated diseases. Because time and funds are limited, and decisions on the best available strategies are required to be made as soon as possible, clinical studies often focus on short-term surrogate parameters. Such surrogate parameters are, for example, the weight or BMI development, but also the development of known risk factors (eg, blood pressure, cholesterol values, etc) for obesity-associated diseases. Thus, to determine the value of an intervention, these short-term surrogates need to be translated into obesity-associated diseases to predict the associated quality of life and cost consequences adequately.

Our research, summarized in this paper, focused on the systematic evaluation, replication, and validation of modeling approaches in the context of obesity. A special emphasis was set on the methodology to translate (short-term) surrogate parameters into (long-term) obesity-associated diseases, which represents a central structural decision to be made when developing a HE obesity model.

> In a perfect world, long-term clinical studies would be performed to evaluate the impact of obesity prevention and treatment measures on chronic obesity-associated diseases.

A stepwise process was followed. First a systematic review was performed to determine which clinical events were commonly simulated in obesity models and how these clinical events were simulated. Hence, all HE models that simulated obesity-associated diseases were included, irrespective of whether events were simulated as acute or chronic health states/conditions or

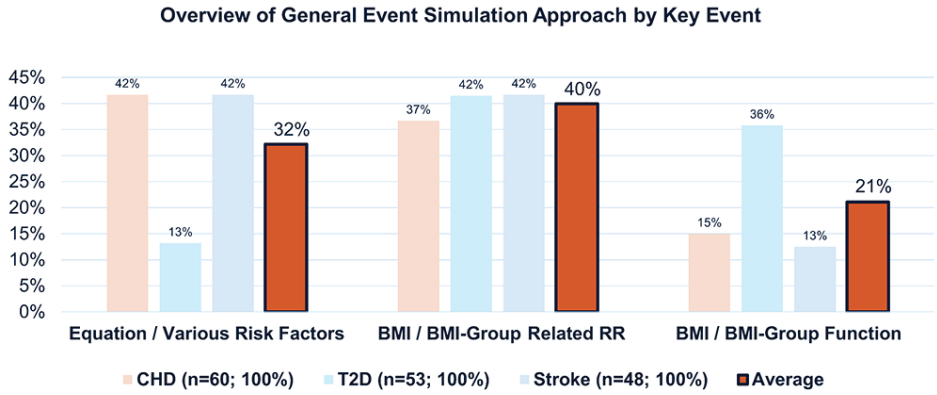
discrete events. The approaches applied to simulate such obesity-associated diseases are named event simulation approaches throughout this manuscript. Second, a replication of high-quality HE obesity models, reflecting the main event simulation approaches, was performed and the reproduction success was evaluated. Finally, using the successfully replicated models, an external validation was performed using state of the art methods applied in comparable research.[6,7] To assess external validation, predicted outcomes were plotted against empirical study endpoints to visually inspect concordance, quantified using linear regression analysis (slope and intercept), categorized deviation from optimal slope (±25%, ±50%, ±100%), and further evaluated using R^2, F test for line identity, and root mean square error (RMSE) for model fit accuracy. Furthermore, the influence of the structural event modeling approach on the HE modeling results was investigated, focusing on the central result parameter of HE assessments, the incremental cost-effectiveness ratio (ICER).

Results

As a result of the systemic literature search, 87 papers reflecting HE obesity models were identified. It was found that most research teams built their own HE model (79%) and that only a minority used a previously published model (21%). Only for a minority (14%) of the model-based HE assessments in obesity was an external event validation was performed.

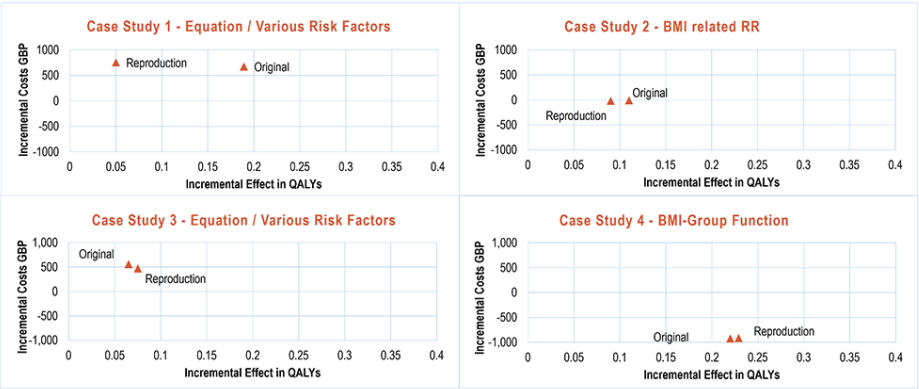
Most frequently simulated clinical events were coronary heart disease (≈83%), type 2 diabetes (≈74%), and stroke (≈66%). These 3 obesity-associated key events were simulated by 39 models (≈54%). As presented in **Figure 1**, we categorized the obesity-associated event simulation approaches into 3 major methodologies, identified as: 1) Equation/various risk factors: established risk functions/equations (eg, Framingham[8,9] or UKPDS[10]) were used to estimate the risk of an event or condition; in these cases the intervention effect was estimated by simulating the intervention's impact on the risk equation's risk factors (such as systolic blood pressure, age, diabetes status, etc); 2) BMI/BMI group–related relative risk: the base risk of the events was estimated using different incidence

Figure 1. Methodological Variations—Event Simulation Approaches in Obesity Models



Abbreviations: BMI, body mass index; CHD, coronary heart disease; RR, relative risk; T2D, type 2 diabetes.

Figure 2. Model Result Reproduction Success—Variations of Incremental Costs and Effects by Case Study



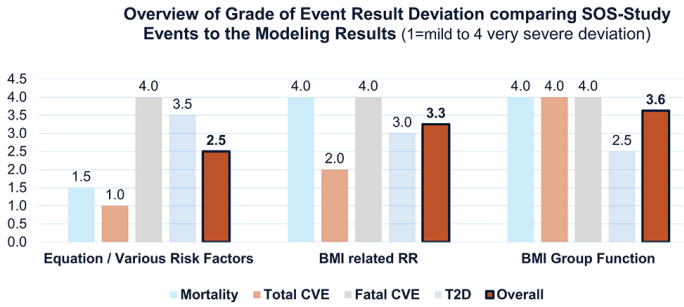
Abbreviations: BMI, body mass index; GBP, British pounds; QALYs, quality-adjusted life years; RR, relative risk.

estimation approaches (potential impact fraction, age, gender, etc) and a BMI or BMI group–specific relative risk (RR) was applied in order to estimate the intervention effect on the frequency of obesity-associated events; 3) BMI/BMI group function: the base risk was estimated on the basis of the BMI or a BMI group (BMI is the central part of the risk equation applied); hence, the intervention effects on the BMI or the BMI group directly impacted the base risk.

In a next step, 4 high-quality HE obesity models[11-14] were selected and a model replication was performed using TreeAge Pro. The model selection process (based on the outcomes of an expert panel consensus[15]) involved satisfying criteria for long-term simulation, specific model types (state transition or discrete event simulation), key simulated events (coronary heart disease, type 2 diabetes, stroke), and applicability to the UK adult population.

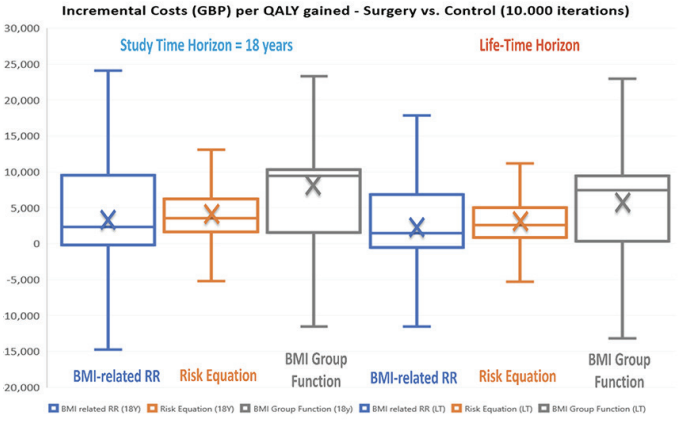
All 4 case studies were state-transition models simulating costs and quality-adjusted life years (QALYs). The reproduction success for model results was measured with several factors.[16] The applied criteria for measuring replication success involved a combination of standards, focusing on achieving identical cost-effectiveness conclusions, ensuring acceptable deviations in individual components (<5%), and obtaining comparable ICERs. As shown in **Figure 2**, incremental costs and incremental QALY visualized on a plane were the key factors for evaluating the combined reproduction success. Accordingly, case study 1 was rated

Figure 3. External Validation Results—Grade of Deviation by Key Event



Abbreviations: BMI, body mass index; CVE, cardiovascular events; RR, relative risk; T2D, type 2 diabetes.

Figure 4. Comparison of Main Incremental Health Economic Outcomes



Abbreviations: 18Y, 18 years study time horizon; BMI, body mass index; GBP, British pounds; LT, lifetime horizon; QALYs, quality-adjusted life years; RR, relative risk.

Table 1. Overview of Mean Health Economic Outcomes

Time Horizon	Approach	Costs (GBP)			Utility			ICER
		Surgery	Control	Incr.	Surgery	Control	Incr.	
18 Years	BMI-related RR	13,695	6598	7097	11.39	9.13	2.26	3143
	Risk Equation	14,410	7834	6576	14.57	12.60	1.97	3338
	BMI Group Function	14,873	4350	10522	10.75	9.49	1.26	8328
Lifetime	BMI-related RR	18,126	10,162	7965	15.37	11.49	3.88	2055
	Risk Equation	26,354	19,637	6717	23.00	20.00	3.00	2241
	BMI Group Function	16,867	6599	10,268	13.92	12.27	1.65	6206

Abbreviations: BMI, body mass index; GBP, British pounds; ICER, incremental cost-effectiveness ratio; RR, relative risk.

as a failure, due to the visualized huge deviation of original and replicated incremental QALY results, and case studies 2, 3, and 4 as successes in reproducing results.

Using the 3 successfully replicated models, an external validation using the Swedish obesity subjects (SOS) study[17] was performed. The SOS study compares long-term health outcomes between individuals who undergo bariatric surgery and those receiving conventional obesity treatments. It was selected as a validation study as it is currently the only available prospective long-term intervention study in obese subjects that has presented statistically significant improvements in mortality, incidence of type 2 diabetes, and fatal/nonfatal cardiovascular events (myocardial infarction and stroke) for obesity surgery compared to matched controls over an 18-year period.

These replicated models reflect 3 main structural event-modeling approaches used in obesity outlined above: 1) Equation/various risk factors; 2) BMI-related RR; and 3) BMI group function. Concordance between modeling results and the SOS study were investigated by linear regression analyses and different measurements (outlined in the methods), and then they were categorized by the grade of deviation observed (from grade 1–4 expressing mild, moderate, severe, and very severe deviations), as presented in **Figure 3**. Overall and by study arm, the risk equation approach showed a better overall event prediction than the BMI-related RR approach, followed by the BMI group function.

To investigate the potential impact of the different event-simulation approaches on the health economic key results, namely the incremental costs the incremental QALYs and the ICER, model simulations were performed comparing surgery versus controls. All models were informed by the same cost and health utility data, extracted from a recent UK NICE appraisal on obesity,[18] as well as by the same population and effect input data from the SOS-study, to ensure comparability. Model simulations were performed for an 18-year SOS-study time horizon and for a lifetime horizon, using Monte Carlo simulations with 10,000 iterations to consider the variation of results. These results are presented in **Table 1** (showing the mean cost, QALY, and ICER results), and in **Figure 4** (showing the ICERs and the deviation of ICERs as boxplots). Considering the mean results presented in **Table 1**, the ICER was lowest for the BMI-related RR approach, followed by the risk equation approach, and was highest for the BMI group function, irrespective of the model time horizon. Looking at these mean results, the BMI-related RR approach consistently demonstrates the best cost-effectiveness, especially as it achieves higher QALYs for its cost difference, compared with the other approaches. Conversely, the BMI group function approach, having the highest costs and lowest QALYs in most cases, generally results in the least favorable ICERs. However, looking at the distribution of the ICER values, presented in **Figure 4**, the different confidence interval levels presented in the box plots are largely overlapping, making the ICER outcomes comparable from a statistical point of view.

Summary and Impact

The findings of our research answered 2 central questions that are strongly connected to trust and confidence in health economic models.

1) How complex does a HE obesity model need to be to adequately predict obesity-associated events? This study suggests that the structure of a HE model matters if clinical events are to be predicted most accurately. Although it was found that none of the structural approaches showed perfect external event validation results, the risk equation approach showed the smallest deviations. Combined with a careful selection of risk equations, this risk equation approach would be the method of choice for a most accurate prediction of obesity-associated events.

2) What impact has the modeling approach on the HE results? If the purpose of an HE model is purely the incremental HE comparison, this study suggests that the structure does not matter much, which seems positive for the credibility and comparability of HE key results based on different structural modeling approaches. The different structural approaches provided comparable probabilistic health economic results, whereas looking at the mean results (in a purely deterministic manner), the categorical BMI approach produced the highest mean ICER and is hence the most conservative estimate from a modeler's perspective (the most cautious in estimating costs, benefits, or outcomes).

> This study suggests that the structure of an HE model matters if clinical events are to be predicted most accurately.

The findings of our research are based on the limitation of using the SOS study as basis. This bases this research on a population of patients with severe obesity (reflected by a mean BMI ≥40 mg/m² in the SOS study population). Furthermore, the surgical approach used in the SOS study is the most invasive and (in the long-term) most efficient intervention approach in obesity. This means that the observed variations in BMI and other risk factors, which are translating into disease risk changes and so into the number of events simulated, related costs, and related QALYs, are strongest for surgery compared to any other less-invasive obesity intervention. Although the surgery option is not representative, it reflects an extreme scenario, in which differences between the investigated structural event simulation approaches should be most pronounced. As in this "extreme scenario" no significant difference was observed, it is likely that these results are transferable to other obesity interventions (such as tirzepatide or semaglutide), although additional research is required to confirm this hypothesis. One key requirement to inform future research in this field are other long-term studies, best representing other obesity interventions, which would allow reperforming this research in a broader population of people with obesity.

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Impact of Nirsevimab for All Infants in Preventing Respiratory Syncytial Virus-Related Hospitalizations and Costs in the Brazilian Private Healthcare System

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Nirsevimab offers effective protection against RSV for all infants, including healthy full-term infants, who account for over 80% of RSV-related hospitalization in Brazil.

Nirsevimab can prevent 5,647 RSV-related hospitalizations and 1,699 pediatric intensive care unit admissions, resulting in an estimated cost savings of BRL 61.5 million in hospitalization expenses.

The results suggest that nirsevimab could substantially reduce the burden and costs of RSV-associated among all infants in the Brazilian private healthcare system.

Implications

Respiratory syncytial virus (RSV) remains a significant cause of morbidity and healthcare burden, particularly in infants. While preterm infants and those with comorbidities face higher individual risks of RSV-related hospitalizations, >80% of these hospitalizations occur in healthy full-term infants. This underscores the importance of strategies to prevent RSV in the broader population. This study showed that nirsevimab can substantially reduce both the burden of RSV-associated hospitalizations and healthcare costs in the Brazilian private healthcare system, preventing 5647 hospitalizations, including 1699 pediatric intensive care unit (PICU) admissions, resulting in savings of BRL 61.5 million with inpatient care.

Introduction

RSV is the most common cause of LRTD in infants and younger children and contributes to substantial morbidity and mortality worldwide. The virus mainly infects children in the first few years of life, with around 50% of children infected during the first year of life and almost all by the age of 2 years.[1] Among children infected during the first year of life, it is estimated that 30% to 70% develop LRTD.[1] In 2019 exclusively, RSV was responsible for an estimated 33 million acute LRTD globally, resulting in 3.6 million hospital admissions and 26,300 in-hospital deaths in children aged under 5 years.[2] Although premature infants and those with underlying comorbidities are among those at highest risk for severe illness, most hospitalizations due to RSV occur in healthy infants born at term.[3]

> There is still an evident lack of nationwide hospitalization and mortality data related to RSV-associated LTRD, highlighting difficulties in defining the priorities and investments needed for prevention and treatment.

In Brazil, RSV was detected in 23% to 61% of infants hospitalized for LRTD.[4] However, there is still an evident lack of nationwide hospitalization and mortality data related to RSV-associated LTRD, highlighting difficulties in defining the priorities and investments needed for prevention and treatment.

The seasonality of RSV varies from temperate to sub-tropical countries and from the Northern Hemisphere to the Southern Hemisphere. Brazil, a continental nation, is the world's fifth-largest country by area and has 3 distinct RSV seasons (**Figure 1**).[5] The season typically begins early in the country's North region in February, followed by

Figure 1.
RSV seasonality in Brazil

the Midwest, Southeast, and Northeast regions starting in March, and finally, the South region beginning in April. On average, each season lasts about 5 months.

Currently, prophylaxis with the monoclonal antibody palivizumab is the only option available in the private Brazilian healthcare system for preventing RSV infection. However, this option is limited to a restricted group: children under 1 year old born prematurely (with a gestational age of up to 28 weeks), children up to 2 years old with lung disease of prematurity or pulmonary dysplasia, and children up to 2 years old with significant congenital heart disease.[6] This leaves a large number of children, especially those up to 1 year of age born at more than 28 weeks gestation, without prophylactic coverage, relying only on infection control measures and supportive therapy. Subsequently, a significant portion of the population remains unprotected against the virus. This includes children with greater vulnerability such as immunocompromised children, children with cystic fibrosis, Down's syndrome, and other conditions not currently covered.

> The present study aimed to evaluate modeled RSV-related hospitalizations and costs of the impact of nirsevimab on the private healthcare system compared to standard of practice (SoP).

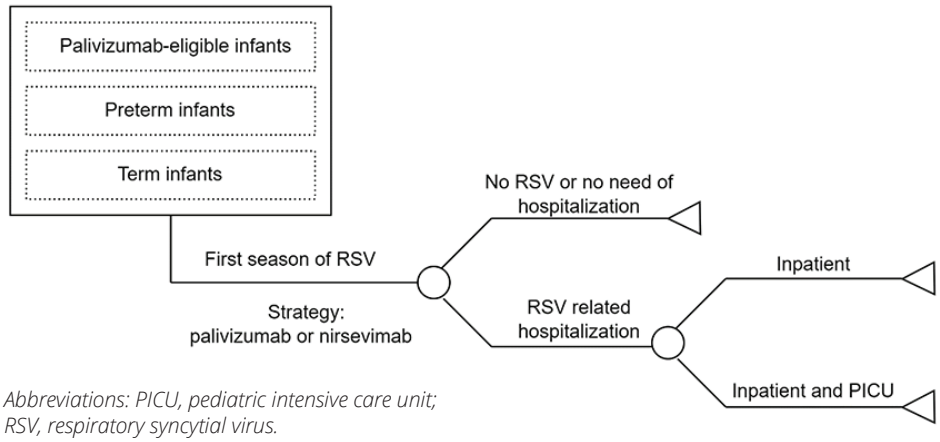
Nirsevimab is a single-dose monoclonal antibody for passive immunization with an extended half-life, which has 70-80% efficacy for the prevention of RSV-associated LRTD in broad infant populations, regardless of gestational age. Nirsevimab has emerged as a safe and effective alternative for preventing lower respiratory tract infections associated with RSV, meeting the need for protection for a wider range of children.[7]

Private healthcare in Brazil consists of private out-of-pocket services and a large private health insurance market. With over 48 million users, representing 24.9% of the Brazilian population, private healthcare plays a significant role in the country's total health expenditure.[8] The present study aimed to evaluate modeled RSV-related hospitalizations and costs of the impact of nirsevimab on the private healthcare system compared to standard of practice (SoP).

Methods

A decision analytic model was used to estimate RSV-associated LRTD events in a Brazilian birth cohort during their first year of life, considering the private payer's perspective (**Figure 2**).[9] Model parameters were derived from published literature and national databases (**Table 1**).[7,10-13] RSV hospitalization rates were based on Hospital Information System from the Department of Informatics of

Figure 2. Decision analytic model structure



Abbreviations: PICU, pediatric intensive care unit; RSV, respiratory syncytial virus.

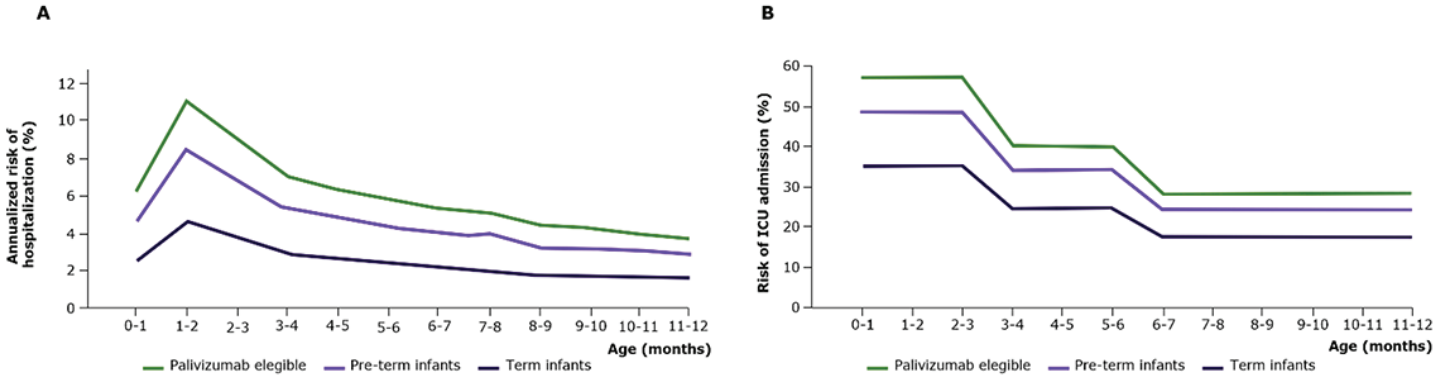
Table 1. Model parameters

Parameter	Value	Source
Individuals <12 months covered exclusively by private care (Brazil 2024)	666,700	IBGE, ANS[11,12]
Palivizumab-eligible infants (<29 weeks or those with comorbidities)	0.84%	SINASC/DATASUS[10]
Late preterm infants (29-36 weeks)	10.45%	SINASC/DATASUS[10]
Full-term infants	88.71%	SINASC/DATASUS[10]
Palivizumab: Risk reduction for hospitalization	86.20%	Model assumption
Nirsevimab: Risk reduction for hospitalization (palivizumab-eligible infants)	86.20%	Simões et al, 2023[7]
Nirsevimab: Risk reduction for hospitalization (preterm and full-term infants)	74.50%[a]	Simões et al, 2023[7]
Palivizumab coverage	59.5%	Model assumption
Nirsevimab coverage	70%	Model assumption
Hospitalization costs (medical ward)	R$5,529.00	Silva et al, 2022[13]
Hospitalization costs (intensive care unit)	R$23,357.00	Silva et al, 2022[13]

Abbreviations: DATASUS, Department of Informatics of the Brazilian Unified Health System (Departamento de Informática do Sistema Único de Saúde); IBGE, Brazilian Institute of Geography and Statistics (Instituto Brasileiro de Geografia e Estatística); SIH: Hospital Information System (Sistema de Informações Hospitalares); SINASC, Information System on Live Births (Sistema de Informações sobre Nascidos Vivos).

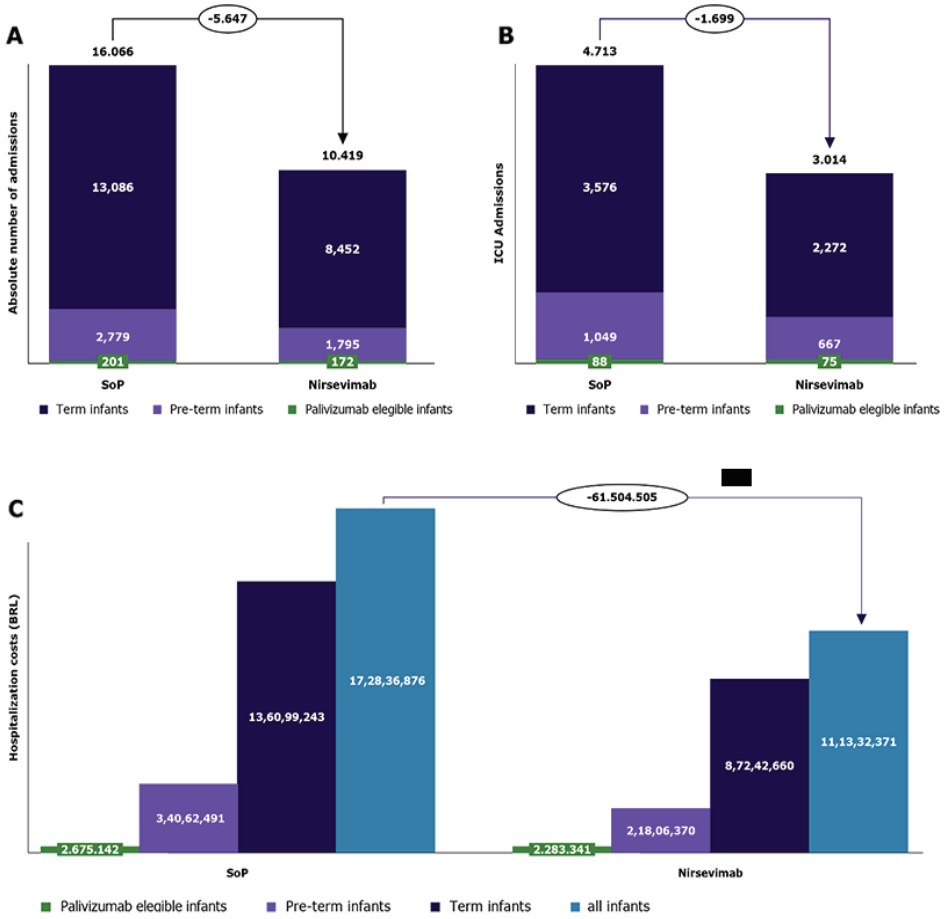
[a] The risk reduction hospitalization with preterm and term infants was conservative; new studies show even higher rates.[5]

Figure 3. Annualized respiratory syncytial virus-related hospitalization rate by gestational age (A) and risk of intensive care unit admission among hospitalized patients (B)



Abbreviations: ICU, intensive care unit.

Figure 4: Number of hospitalized patients by gestational age (A) and number of intensive care unit–hospitalized patients by gestational age (B), and hospitalizations costs (in BRL[a]) by gestational age



Abbreviations: BRL, Brazilian real; ICU, intensive care unit; SoP, standard of practice.
[a]1 USD = 5.17 BRL, April 25 2024, central bank of Brazil. Source: https://www.bcb.gov.br/.

the Brazilian Unified Health System (SIH/DATASUS),[10] adjusted for gestational week at birth according to published literature (**Figure 3**).[14] Intensive care unit (ICU) admission risk was based on published literature. Based on Brazilian market data, we assumed a prophylaxis coverage rate of 70% with nirsevimab and 59.5% with palivizumab (corresponding to a mean of 4.25 doses received by 70% of infants). To be conservative, the risk reduction for hospitalization for palivizumab was assumed to be the same as nirsevimab achieved in published studies.

Results

This model predicts that 58.1% of RSV-related hospitalizations occur during the RSV season, while the remaining 41.9% occur outside the season (**Figure 4**). Based on the SoP, it is estimated that there will be 201 RSV-related hospitalizations for palivizumab-eligible infants, 2779 for late preterm, and 13,086 hospitalizations for full-term infants. Additionally, the model predicts 4712 admissions to the PICU due to RSV.

> Nirsevimab is designed to provide long-lasting protection to all infants, regardless of gestational age.

In the modeled scenario, nirsevimab prevented 5647 hospitalizations, with 29 in palivizumab-eligible infants, 984 in late preterm infants, and 4634 in full-term infants. These prevented hospitalizations

also included 1699 PICU admissions. The model suggests that by preventing RSV-related hospitalizations, nirsevimab had the potential to save nearly Brazilian real (BRL) 61.5 million. This includes BRL 0.4 million for palivizumab-eligible infants, BRL 12.3 million for late preterm infants, and BRL 48.9 million for full-term infants (**Figure 5**). These savings do not account for outpatient care and social costs.

Sensitivity analysis showed consistent results when different coverage rates were applied. An absolute reduction of 10% in the estimated coverage of nirsevimab (from 70% to 60%) would result in savings of BRL 52.5 million and prevent 4827 hospitalizations (including 1450 in the ICU); an absolute increase of 10% (from 70% to 80%) would result in savings of BRL 70.5 million and prevent 6466 hospitalizations (including 1947 in the ICU).

Conclusions

While preterm infants have a higher individual risk of hospitalization, term infants account for nearly 80% of the total number of RSV-related hospitalizations. This underscores the importance of strategies to prevent RSV in the broader population.

Nirsevimab is designed to provide long-lasting protection to all infants, regardless of gestational age. After developing this analysis, other studies were published confirming that nirsevimab has superior efficacy in reducing the risk of hospitalization.[5,15-17]

Nirsevimab could substantially reduce RSV-related hospitalization burden and costs. This study offers information for policymakers and healthcare managers to evaluate the potential benefits of reimbursing nirsevimab into RSV prophylaxis strategies. Further research is necessary to assess the impact of nirsevimab in the Brazilian private setting.

Funding

This study was sponsored by Sanofi and AstraZeneca. Nirsevimab is being developed and commercialized in partnership between Sanofi and AstraZeneca.

Conflicts of Interest

SW, JS, KR, AT, AK are Sanofi employees, and may hold stock and/or stock options in the company. MF and NBS received professional service fees from Sanofi for conducting this research. MAPS and RTS participated in advisory board for Sanofi.

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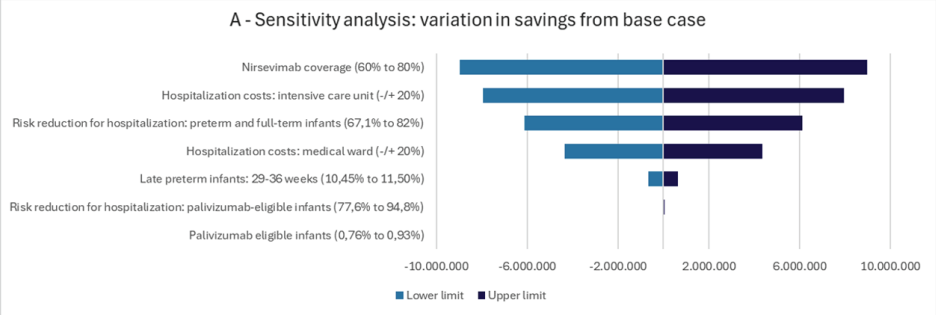
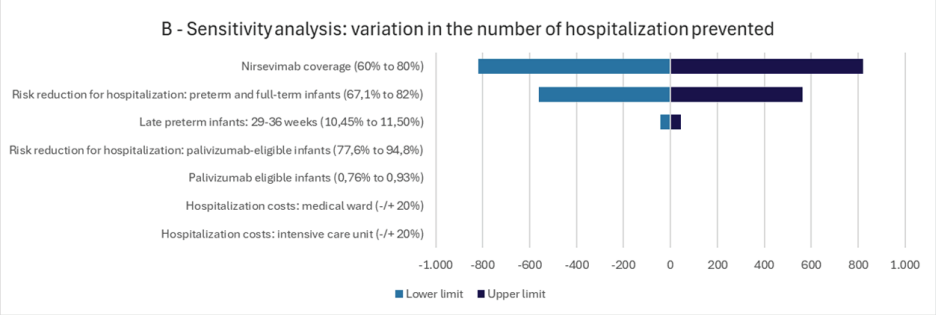
Figure 5. Univariate sensitivity analysis. (A) variation in savings; (B) variation in the number of hospitalizations prevented



Parameter	Lower Limit	Upper Limit
Nirsevimab coverage (60% to 80%)	-52.541.012	-70.467.996
Hospitalization costs: intensive care unit (-/+ 20%)	-53.569.328	-69.439.680
Risk reduction for hospitalization: preterm and full-term infants (67.1% to 82%)	-55.393.234	-67.615.774
Hospitalization costs: medical ward (-/+ 20%)	-57.138.779	-65.870.229
Late preterm infants: 29-36 weeks (10.45% to 11.50%)	-60.854.565	-62.154.443
Risk reduction for hospitalization: palivizumab-eligible infants (77.6% to 94.8%)	-61.465.324	-61.543.684
Palivizumab eligible infants (0.76% to 0.93%)	-61.511.679	-61.497.329



Parameter	Lower limit	Upper limit
Nirsevimab coverage (60% to 80%)	-4.827	-6.466
Risk reduction for hospitalization: preterm and full-term infants (67.1% to 82%)	-5.085	-6.209
Late preterm infants: 29-36 weeks (10.45% to 11.50%)	-5.603	-5.691
Risk reduction for hospitalization: palivizumab-eligible infants (77.6% to 94.8%)	-5.644	-5.650
Palivizumab eligible infants (0.76% to 0.93%)	-5.648	-5.645
Hospitalization costs: medical ward (-/+ 20%)	-5.647	-5.647
Hospitalization costs: intensive care unit (-/+ 20%)	-5.647	-5.647

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Q&A

Driving Meaningful Change in the Healthcare Landscape in Latin America

Interview With Karla Alcazar, MBA

President and General Manager, LATAM, Eli Lilly

> "I have dedicated my entire career to the pharmaceutical industry because of my passion for making a meaningful difference in patient health."
>
> – Karla Alcazar

Karla Alcazar, MBA, Head of LATAM at Eli Lilly, discusses the company's plans to tackle pressing regional health challenges such as obesity, diabetes, and cancer, while also highlighting the region's critical role in Lilly's global strategy. Alcazar offers insights into the company's focus on innovation, diversity, and patient-centricity, as well as her efforts to empower female talent and drive meaningful change in the LATAM healthcare landscape.

PharmaBoardroom: What led you to this role as the LATAM Head of Lilly? What were your primary goals in leading this region?
Karla Alcazar: I have dedicated my entire career to the pharmaceutical industry because of my passion for making a meaningful difference in patient health. My journey began in Mexico, where I aimed to impact local healthcare, but I have since been fortunate to contribute to improving health globally.
As the President and General Manager of LATAM, I oversee the entire region while directly managing the Mexican business. I am the first woman in this role and have been here for 2 and a half years. I also serve as Vice President of the industry association in Mexico, which has been a rewarding opportunity to contribute to broader healthcare discussions.

When I took on this role, my main priority was driving growth through new products. At the time, the business was heavily reliant on mature brands, as they were the largest contributors to sales. However, I believed that our focus needed to shift toward the future.

I set a clear goal to deliver double-digit growth. To achieve this, we redirected investments away from mature brands and concentrated on launching and scaling our newer products. Today, we are proud to be one of the few companies in the Mexican market achieving double-digit growth, effectively double the average growth rate of the overall market.

My second focus was talent development. We established an ambitious talent agenda to build and nurture the capabilities within our Mexican business. I am thrilled that we are now starting to see the results, including successfully exporting several team members to corporate roles. This has been a point of pride for our organization and a testament to the strength of our people.

PB: As Lilly aims to become the world's first trillion-dollar life science company, with plans to launch over 20 new drugs in the next decade—an average of two per year in Latin America—how are you preparing for this upcoming period of product launches?
KA: The key to preparing for this ambitious period is mindset. The team must be ready for launch, and we've made significant changes to how we approach this. Previously, we would begin our launch preparations about 12 months before the actual launch. Now, we are starting much earlier to set the groundwork. This is especially important because many of our upcoming launches are for first-in-class or best-in-class drugs, which often require us to create new markets entirely.

Take Alzheimer's disease as an example. Before we even think about treatment, we need to build an ecosystem that fosters diagnostics and raises awareness about the disease itself.

Similarly, for conditions like obesity, we are working to address the stigma and misconceptions surrounding it. Many still view obesity as a lifestyle choice rather than a chronic disease, but it is a condition with serious health consequences. By starting early, we aim to ensure that the healthcare ecosystem—diagnostics, awareness, and key stakeholders—are ready by the time we launch.

PB: What has been your experience in managing the expectations of key stakeholders regarding the benefits of new products, particularly in the Mexican market, which faces significant challenges related to obesity?
KA: There is still a significant opportunity to change how we approach obesity. What makes me optimistic is that in the Mexican market, many leaders in the healthcare space now recognize obesity as a pandemic. With two-thirds of the adult population classified as overweight or obese, this is a crisis affecting not only individuals but also the healthcare system, which bears enormous costs from related conditions like cardiovascular disease and many others.

> Today, we are proud to be one of the few companies in the Mexican market achieving double-digit growth, effectively double the average growth rate of the overall market.

However, we still face the challenge of shifting the belief that obesity can be resolved solely through prevention, exercise, and dieting. While prevention is critical, it is not a complete solution. Many patients follow diets, exercise diligently, and yet struggle to lose weight because obesity is a chronic disease. It must be treated as such.

At Lilly, we advocate for prevention but also recognize the urgency of addressing obesity as a chronic condition. The stigma surrounding obesity needs to end. Many factors, including genetics and environmental influences, contribute to its prevalence. With two-thirds of Mexico's population already overweight or obese, we need a paradigm shift in how we approach this issue.

PB: With competitors in the market, how does Lilly maintain a competitive edge in this segment?
KA: Lilly's focus is twofold. First, we are committed to developing the most effective treatments. Our research and development efforts are dedicated to ensuring that our medications deliver the best outcomes for patients. Second, we emphasize working closely with key stakeholders to drive meaningful change in the perception and management of obesity.

We are not here to simply promote weight loss or to encourage the misuse of these medications. Our mission is to help patients who are at serious risk of health complications and even death due to obesity. By focusing on the patients who truly need treatment and ensuring ethical practices, we aim to lead the market responsibly and with purpose.

PB: Diabetes is another critical health issue in Mexico and across Latin America. What more can be done to address the diabetes crisis in Mexico and the broader region?
KA: The first step is working closely with healthcare professionals. There is a significant opportunity here because many patients remain undiagnosed. At the same time, even those who are diagnosed and treated are often not achieving proper control of their condition. Lilly can play a key role by educating healthcare providers, not just about new therapies but also about the importance of treating diabetes early and effectively.

We need to move away from the outdated approach of starting with older treatments and waiting too long to adopt newer, more effective options. Diabetes is a progressive disease, and patients deserve the best care from the outset. Today, only about 10% of treated diabetes patients are actually in control of their condition. This represents a tremendous opportunity to make a meaningful impact on the lives of patients while reducing the immense costs that diabetes imposes on both healthcare systems and individuals paying out of pocket.

PB: Digital tools and devices are really improving the lives of patients, especially in managing diabetes. Where do you feel Latin America stands on that front?
KA: Latin America is making strides in this area. I was reading that there are around 1200 digital health companies in the region, with the majority based in Brazil, but also a growing presence in Mexico. Globally, health systems are recognizing that digital tools can help address critical challenges like resource limitations.

Telemedicine, monitoring devices, and other digital solutions can alleviate the strain on physical healthcare resources. These tools allow for more efficient management of conditions like diabetes, where timely interventions are crucial. Patients no longer have to wait as long for consultations or routine follow-ups, which is a significant improvement for both the system and the patients. The digital health environment in Latin America is evolving and has the potential to drive greater efficiency and better outcomes.

PB: When it comes to access to innovation and medicine, do you believe Latin America fully recognizes the value of innovation in healthcare?
KA: I believe there is a genuine commitment from governments

and key stakeholders to provide the best possible healthcare to their populations. However, significant challenges remain. For instance, in Mexico, only 5.5% of gross domestic product is spent on healthcare, which is far below the Organization for Economic Cooperation and Development´s recommended minimum of 9.2%. While countries like Brazil and Colombia invest a bit more, they are still below that benchmark. This presents a substantial opportunity for improvement.

Another challenge is the delay in making innovative treatments available to patients. It can take 4 to 5 years for new therapies to reach those in need. Imagine knowing that a life-saving treatment exists but not being able to access it for years. It is heartbreaking for patients and their families, and this is something that must change.

We also need to shift the focus from solely looking at the cost of innovation to understanding its broader impact. Innovative treatments improve quality of life, reduce hospitalizations, prevent complications, and boost workplace efficiency. These factors drive economic growth and reduce long-term healthcare costs. While there is growing recognition of the importance of health, we must continue to advocate for policies and systems that prioritize health as a fundamental driver of economic and societal progress.

PB: What other key therapeutic areas is Lilly focusing on in the Latin American region?
KA: Lilly's oncology franchise is a significant focus for the region, particularly in the area of breast cancer. Right now, we are commercializing treatments for breast cancer with a clear vision to make it curable in cases where it is diagnosed and treated early. The ultimate goal is to truly say we have cured cancer for some patients.

Beyond breast cancer, we have a robust pipeline of around 60 molecules in development across oncology. Some of these continue the focus on breast cancer, while others target lung cancer and explore cutting-edge areas such as gene therapy and precision medicine. These advancements aim to deliver more specialized treatments tailored to individual patient needs. While breast cancer remains the cornerstone, these additional areas are poised to play a transformative role in our offerings.

PB: How important is the Latin American region for Lilly's overall strategy, and what role does it play in the company's global growth?
KA: Latin America, particularly Brazil and Mexico, plays a critical role in Lilly's global strategy. These two markets are among the company's top 12 globally and are projected to climb higher, potentially reaching the top 10. The region's significance stems from the immense unmet healthcare needs, particularly in areas like diabetes and obesity, where prevalence rates are some of the highest in the world.

Our goal is ambitious but achievable—to triple our business in Latin America within the next 5 years. This growth aligns with the tremendous demand for innovative solutions in the region and Lilly's robust pipeline, which is perfectly positioned to meet these needs. We are launching at least 2 new products annually and are already working across 5 major business units—cardiometabolic health, diabetes and obesity, Alzheimer's, immunology, and oncology. With one of the most promising pipelines in the industry, we are well-prepared for this period of accelerated growth.

PB: As the first female leader of Lilly in the region, how are you working to empower the next generation of female talent in the pharmaceutical industry?
KA: Empowering the next generation of female talent starts with being a visible role model. This is why, despite my busy schedule, I take on leadership roles both within Lilly and the broader pharmaceutical industry.

I dedicate a significant amount of time to mentoring, both within and outside Lilly. Within the company, we emphasize equality in recruitment processes by ensuring gender balance among candidates for every position. While we always select the best candidate for the role, we guarantee that women have an equal opportunity to compete. Once women join Lilly, we focus on their growth through structured succession planning. This focused approach has yielded tangible results—half of our leadership team in the region is now composed of women, who are themselves driving empowerment for others.

> I believe there is a genuine commitment from governments and key stakeholders to provide the best possible healthcare to their populations. However, significant challenges remain.

Additionally, I believe in engaging men in the conversation about gender equity. I am the proud mother of a son, and I recognize the importance of raising boys who value and support women. In Lilly's women empowerment initiatives, we invite men to share their perspectives as supportive partners and managers. My own career has been shaped by male mentors who believed in me and encouraged me to take on challenges, such as pursuing an MBA or moving to Brazil.

Diversity is not just about fairness—it directly impacts business outcomes. Companies benefit economically and strategically from diverse teams. By empowering women, we are driving better decisions and stronger performance across the board.

PB: What final message would you like to share with our global readers about your vision for Lilly and the healthcare sector in Latin America?
KA: Lilly has been a part of Latin America for over 80 years—we just celebrated our 81st anniversary this year—and we remain fully committed to the region. Our focus is on launching innovations that will improve health outcomes and enhance the quality of life for people in Mexico and across Latin America. We see a bright future ahead and are dedicated to being a transformative force in healthcare for many decades to come. Together, we can continue to make meaningful progress in addressing the region's most pressing health challenges and delivering hope to millions of patients.

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