SEPTEMBER/OCTOBER 2024 VOL. 10, NO. 5

VALUE & OUTCOMES SPOTLIGHT

A magazine for the global HEOR community.

MAKING AN IMPACT ON HEOR

ISPOR
Improving healthcare decisions

VALUE & OUTCOMES SPOTLIGHT

SEPTEMBER/OCTOBER 2024
VOL. 10, NO. 5

VALUE & OUTCOMES SPOTLIGHT

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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The Transformative Impact of HEOR

Health economics and outcomes research (HEOR) is a rapidly evolving field that has become increasingly relevant in today's complex healthcare landscape. The discipline's primary goal is to inform healthcare decision making by providing scientifically rigorous and sound data on health economics and outcomes. The impact of HEOR is far-reaching, influencing healthcare stakeholders, addressing challenges, and informing issues using data and research approaches.

ISPOR has been at the forefront of this evolution, making significant strides in the application of HEOR to transform healthcare. Former ISPOR president, Jan Elias Hansen, PhD (2022 – 2023), highlighted the Society's achievements in her term, emphasizing the role of HEOR in engaging healthcare stakeholders, addressing pain points, and proactively informing healthcare issues.

One of the key impacts of HEOR is its role in informing regulatory approval with real-world evidence (RWE). For instance, noninterventional real-world data studies and registries have been used to inform regulatory approvals in various therapeutic areas such as oncology, neuroscience, and infectious diseases. This impact has been particularly evident in the United States, where RWE has been instrumental in providing access to innovative drugs.

HEOR has also made significant strides in other parts of the world. In Argentina, real-world data were used in developing and implementing a performance-based risk-sharing agreement for patients with HR+ and HER2- advanced or metastatic breast cancer. This work has had a profound impact on patients' access to novel treatments.

> ISPOR has been at the forefront of this evolution, making significant strides in the application of HEOR to transform healthcare.

ISPOR's influence is also evident in the development of national guidelines in countries like India, New Zealand, and Thailand. ISPOR chapters in these countries have been contributing expertise and directly engaging in the development of national guidelines for health technology assessment, pricing, reimbursement, and economic evaluations.

However, the impact of HEOR is not just limited to policy making and regulatory approvals. It also plays a crucial role in shaping the conversation about the value of healthcare. As pointed out in the feature article, HEOR scientists need to become better communicators about what they do, how they do it, and why non-HEOR experts should care.

> ISPOR Student Chapters are having a significant impact on the growth of the HEOR profession and its relevance around the globe, as evidenced by their activities and achievements.

One of the ways to achieve our goals is by making the impact of HEOR more concrete. For instance, Jalpa Doshi, PhD, and her team used rigorous HEOR and policy methods to propose policy solutions to fix Medicare Part D cost-sharing policy to enhance access to specialty drug treatments. Their work highlighted the financial burdens on patients and proposed solutions like an annual out-of-pocket cap combined with monthly payment caps (smoothing). This research influenced policy changes in the Inflation Reduction Act of 2022, set to take effect in 2025 and is a testament to the power of HEOR in shaping healthcare policy and improving patient outcomes.

Emphasizing the need for HEOR scientists to improve their communication skills is also critical. Darius Lakdawalla, PhD, from USC Schaeffer Center discusses the importance of explaining the value of medical innovations in concrete terms that resonate with the public. He highlights the need to frame HEOR findings in terms of human values like life expectancy and health outcomes. Dr Lakdawalla's work on Medicare coverage for obesity treatments and the economic impact of drug-pricing measures exemplifies the need for clear and relatable communication. Additionally, Jens Grueger, PhD, from Boston Consulting Group stresses the importance of using simple language and broader perspectives in communication. He also suggests training young HEOR professionals in effective communication to ensure their research influences health policy and public understanding.

ISPOR Student Chapters are having a significant impact on the growth of the HEOR profession and its relevance around the globe, as evidenced by their activities and achievements. For example, in 2023, the ISPOR Student Chapter based at King Saud University in Saudi Arabia organized a visit to the Saudi Food and Drug Administration's Pricing Department, where 30 students gained practical insights into the regulatory aspects of the pharmaceutical industry. In India, the ISPOR Manipal University Student Chapter organized the ISPOR India Student Chapter Conference in February 2024, which provided a platform for ISPOR thought leaders, innovators, and professionals from around the country and region to come together to share their insights and discuss the topic, "Patient Engagement in Healthcare: Asian Perspective." These are just a few examples of the powerful impact ISPOR student chapters are having globally.

In conclusion, the impact of HEOR is transformative and far-reaching. It is not just about generating evidence or informing policy decisions; it is about making a real difference in the lives of patients. As we move forward, it is crucial that we continue to leverage the power of HEOR to transform healthcare, improve patient outcomes, and ensure equitable access to high-value treatments. The work of ISPOR and its members serves as a beacon, guiding us toward a future where healthcare decision making is informed, evidence-based, and patient-centered.

We would love to highlight your stories in a future issue of *Value & Outcomes Spotlight*. I invite you to share your HEOR story of impact via this submission link.

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

Highlighting HEOR Innovation and Impact

Rob Abbott, CEO & Executive Director, ISPOR

This issue of *Value and Outcomes Spotlight* comes at an interesting time for health economics and outcomes research (HEOR) professionals. Over the past year, the leaders of several HEOR groups in global biopharmaceutical firms have been let go and the balance of the teams has been dispersed into other functions, typically Market Access or Medical Affairs. Corporate reorganizations are nothing new, but the targeted reorganization of HEOR groups coincides with several important changes within the healthcare landscape. Regulatory expectations for evidence are both increasing and broadening (clinical, economic, patient-centered), the use of artificial intelligence (AI) and digital tools is growing, and there is a push for acceleration in drug development. Meantime, patients are clamoring for accessible, affordable, and effective drugs. Globally, the story is much the same. Populations are aging in many countries and the demand for novel medicines is on the rise. To obtain coverage or reimbursement, companies have to prove that their products both improve on the standard of care *and* are more cost-effective. Clearing this "4th hurdle," as it is often called, has never been more important, or difficult, for biopharma. The recent round of layoffs and restructuring of HEOR groups is therefore interesting, to put it politely, because there is some truth to the adage that "there is no access without evidence" and HEOR scientists are the primary generators of that evidence.

> The way ahead for HEOR needs to be built on the generation of scientifically robust evidence that stands up to the scrutiny of payer organizations–and provides guidance to clinicians, regulators, patient organizations, and other stakeholders.

I therefore welcome the discussions that have been curated for this issue of VOS. I believe that by clearly explaining what HEOR is (and isn't), where and how it advances drug or product development, and perhaps most importantly, where it can be shown to have influenced healthcare decision making, we honor the men and women who work so hard to generate evidence of real value. As my colleague, Scott Ramsey puts it: *value is not about getting something cheap; it's about bringing the best that medicine has to offer to the largest number of people at reasonable cost.* The way ahead for HEOR needs to be built on the generation of scientifically robust evidence that stands up to the scrutiny of payer organizations—and equally, provides guidance to clinicians, regulators, patient organizations, and other stakeholders. HEOR scientists have precisely the skill set needed to do this and demonstrate what represents value and what doesn't.

How to get started? As a first step, the HEOR profession needs to tell stories of innovation and impact. As an example, in 2007, Pfizer and Bristol-Myers Squibb began development of apixaban as an anticoagulant. The product we know today as Eliquis is used to treat and prevent blood clots and prevent stroke in people with nonvalvular atrial fibrillation. It is on the World Health Organization's List of Essential Medicines and in 2021 was one of the most commonly prescribed medications in the United States with more than 17 million prescriptions. What is less well known is that Eliquis' global success revolved around the real-world evidence generation and access strategies that were carefully designed and executed by HEOR scientists. The same is true for antiretroviral therapy for HIV in the United States. The use of 3 or more antiretroviral medicines (1 pill)—commonly called the HIV "cocktail—is currently the standard treatment for HIV infection largely due to the HEOR cost-offset and budget projection work enabling appropriate funding of drug assistance programs at national and state levels. More generally, HEOR has been instrumental in label expansion—demonstrating the clinical and financial efficacy of a product developed for one patient population in another. The common denominator in each of these examples is the pivotal role that HEOR played in bringing a product to market.

ISPOR has recently launched a bold new strategy anchored by a vision of "a world in which healthcare is accessible, effective, efficient, and affordable for all."[1] We will realize this vision by leveraging HEOR to improve evidence-generation methods and the speed with which they are deployed; by converting health data from sources like wearables and electronic health records into useful evidence that can shape healthcare decisions; and by reaching out to our industry and other partners to better understand their pain points and where HEOR can address them. The scientific disciplines that underpin HEOR offer tremendous power, rigor, and credibility to C-suite executives,

> Ultimately there is no single (or simple) algorithm that fosters better healthcare decisions, but I'm convinced that the multidisciplinary science that is HEOR offers the best chance to move the needle forward.

especially now, if they increase their fluency in it. Among other benefits, HEOR, when done strategically and in the context of a company's broad business objectives, can pull the right

[1] The new strategy can be accessed at www.ispor.org

data together to reduce uncertainty. ISPOR will be the primary catalyst in the development and communication of HEOR evidence to support this work—it benefits all of us with an interest in improving healthcare.

Moving forward, HEOR needs to be recast not as an academic or purely scientific exercise exclusively, but rather as a multidisciplinary body of work that can be a key agent of innovation in healthcare. The stories of innovation and impact gathered here do a wonderful job of illustrating how this is being done today and how HEOR can grow its impact tomorrow. I'm especially excited by the ways in which HEOR is incorporating AI capabilities through generative AI and large language models to enhance real-world data analyses, model programming, and literature reviews. Ultimately there is no single (or simple) algorithm that fosters better healthcare decisions, but I'm convinced that the multidisciplinary science that is HEOR offers the best chance to move the needle forward.

ISPOR NEWS

Training Patients to Be Effective Stakeholders in the EU HTA Process

Finn McCartney MA, Aikaterini Charapa MA, Maria Dutarte MA, Sarah Bernier MA and HTA4Patients Project Consortium, EUPATI, Utrecht, The Netherlands

What is the EU HTA regulation?

The process of how health technologies are assessed in the European Union (EU) is changing; the EU Health Technology Assessment Regulation (HTAR) will come into effect in 2025 with the aim of harmonizing and simplifying the clinical assessment of a given health technology via Joint Scientific Consultations (JSC) and Joint Clinical Assessments (JCA).

These joint assessments will be performed by an appointed subgroup of members from the Health Technology Assessment Coordination Group (HTACG), which includes a group of representatives from the Member States. The regulation means that cooperation across the European Union is mandated and that one centralized system will be in place for health technologies to be assessed. This has the additional benefit of eliminating the need for duplicating work for multiple national HTA processes (normally a health technology developer would submit the same information to several HTA bodies separately). Also, the produced JCA reports must be given due consideration by a given member state in their respective national HTA processes for a given health technology (**Figure 1**).

What does this mean for patients in the EU?

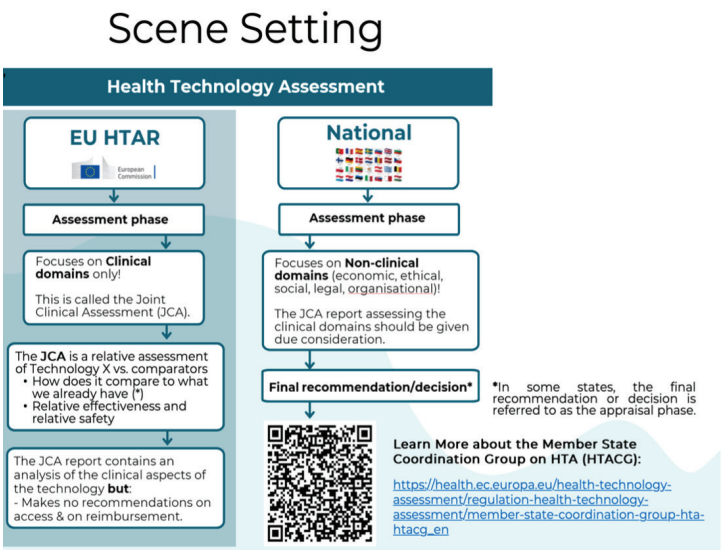
The EU HTAR has made patients and patient organizations key stakeholders that will need to be consulted throughout an EU HTA. There are several mechanisms and opportunities for these stakeholders to provide input in this process at the national and European levels.

> The regulation means that cooperation across the European Union is mandated and that one centralized system will be in place for health technologies to be assessed.

In the JCA, illustrated in **Figure 2**, patients will be involved in the scoping process (PICO questions) and they will be able to provide input in the draft (JCA) report. These steps will be crucial for patient involvement since patients can provide insights of their own experiences, needs, and perspectives or the multiple experiences, needs, and perspectives of the patient group(s) they represent.

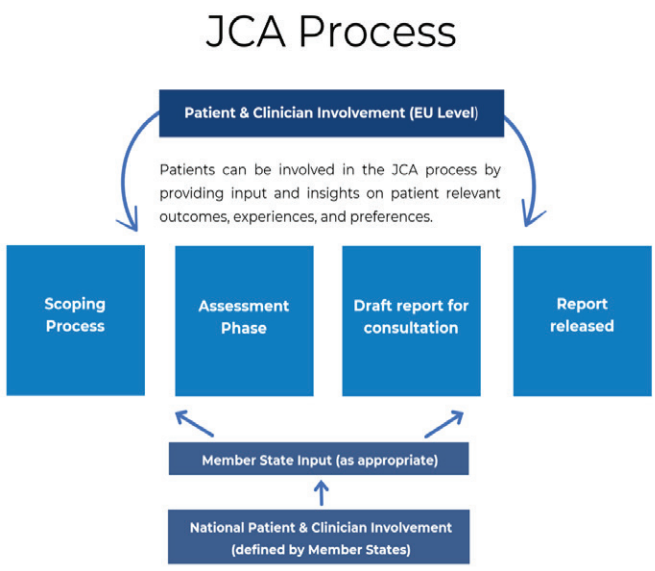
As of 2023, patient organizations are also the largest group represented in the Stakeholder Network—a formal part of the regulation that facilitates dialogue between European umbrella stakeholder organizations and the HTACG.

Figure 1: Overview of how health technology assessment will work from 2025 onwards in the European Union



EU indicates European Union; HTA, health technology assessment; HTAR, Health Technology Assessment Regulation; JCA, Joint Clinical Assessment.

Figure 2: Illustration of how patients can be involved in the Joint Clinical Assessment at the European and national levels



EU indicates European Union; JCA, Joint Clinical Assessment.

Patient organizations in this network (**Figure 3**) will play a crucial role in providing input to the HTACG's annual work program, annual report, and identifying patient experts who will be relied upon during the joint work (JSC & JCA). This is one of several mechanisms and opportunities for these stakeholders to provide input in this process at the national and European levels.

What are the remaining challenges that patients' have identified?

The European Patients' Academy on Therapeutic Innovation (EUPATI) is committed to providing information and training on health innovation to patients and patient representatives, focusing on their involvement in these processes, including HTA. In 2023, EUPATI launched an EU-funded project, HTA4Patients, focusing on building knowledge among patient communities around the HTAR.

Within the framework of this EUPATI project, when interacting with these groups, patients have expressed their difficulty in accessing such a complex topic like HTA: how it works and relates to their personal treatments and patient journey, why does it matter, and the technical jargon associated with this topic.

EUPATI has observed a clear gap in the knowledge and capacity about the EU HTA process and the subject of HTA more generally. For patients to be fully informed, they need training on what is changing in the EU HTA landscape and how they can prepare for this new reality.

What resources can patients access to learn more about the EU HTAR?

To build capacity within the patient community, the European Commission (EC) (HADEA/EU4Health) is funding the above-mentioned EUPATI HTA4Patients project as well as EUCAPA (coordinated by EURORDIS) with the goal of producing educational resources and training on the new regulation.

Through the HTA4Patients Project, EUPATI and its partners have cocreated a free e-learning course, EU Health Technology Assessment Regulation (HTAR), and will be organizing online training sessions on the HTAR for patient groups. Both these materials were created by authoring groups comprising representatives of EUPATI Fellows (patient experts), partners (including ISPOR), EUPATI National Platforms, and other members of its wider network. Since its inception, EUPATI has used this multistakeholder approach to put patients at the center of the discussions and guarantees that our resources are both scientifically reliable and in patient-friendly language.

> To build capacity within the patient community, the European Commission is funding EUPATI's HTA4Patients with the goal of producing educational resources and training on the new regulation.

In each lesson of the online course, the learner is taken through each element of the process and the information has been presented in a variety of forms to engage the reader. At the end of the course, the learner can take an assessment to obtain a certificate that they have completed the course. Like all EUPATI's courses, they are freely accessible and can be accessed anywhere in the world. This is one of many ways patients can prepare themselves for the EU HTA process.

EUPATI is now in the process of planning for the online training sessions that will run from October 2024 until September 2025. Patient organizations interested in having EUPATI run a tailored training session for them can express their interest here.

Also, the online course and training materials will be translated into Czech, French, Greek, German, and Spanish by summer 2025. These translations will maximize the reach of these training materials in the patient community.

As of August 2024, the English version of the course has already been accessed by over 2500 unique learners. This shows that the patient community is already preparing themselves for 2025 and it is critical that they are made aware and receive training on the EU HTA process now and as it evolves.

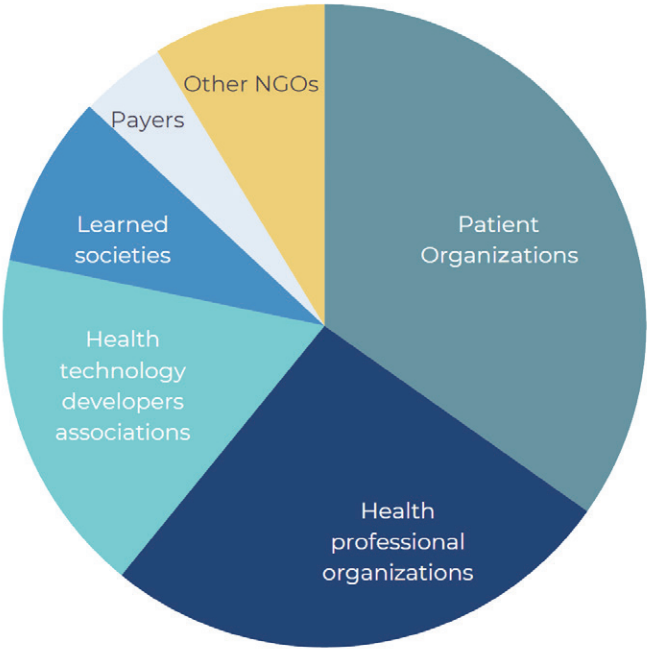
How can patients prepare for 2025?

In addition to training, there are several ways patient stakeholders can prepare themselves for the EU HTAR. The following is a checklist for patients, patient representatives, and patient organizations prepared by EUPATI as part of the HTA4Patients project:

(1) Strengthen your network:

- Check the EMA's list of eligible patient organizations
- Connect with relevant patient organizations
- Check who is in the stakeholder network
- Connect with EUPATI national platform

Figure 3: Makeup of stakeholder network



Source: European Commission.
NGO indicates nongovernmental organization.

(2) Build your capabilities:
- Familiarize yourself with HTA fundamentals
- Familiarize yourself with EUCAPA and HTA4Patients training
- Learn more about PICOs
- Get familiar with conflict of interest examples
- Sign up for relevant newsletters
- Visit the EC's latest updates

(3) For patient organizations:
- Get to know the HTAR and legislative framework
- Familiarize yourself with the regulatory frameworks for marketing authorizations (EMA)
- Become a member of the stakeholder network, if eligible
- Participate in public consultation on the Implementing Acts
- Organize training for your members

Continued commitment to patient involvement

HTAR presents a challenge but also an opportunity for patient involvement in HTA. In partnership with ISPOR and other members of its multistakeholder network, EUPATI is committed to enhancing efforts within health literacy and patient education in the area of HTA. Through an effective, innovative, and collaborative model of cocreation and codelivery of training, long-standing impact can be created in this space.

Acknowledgments: We would like to acknowledge that the HTA4Patients materials for the online course and training sessions were made possible due to the work carried out by members of the Authoring Group, Training Group, Editorial Board, Project Management Group & Project Expert Panel.

ISPOR Conferences and Events

ISPOR Europe 2024 | 17-20 November

Barcelona International Convention Center, Barcelona, Spain

ISPOR Europe 2024 has become THE not-to-be-missed European conference of the year with a host of thought-provoking sessions and opportunities to immerse yourself in the health economics and outcomes research (HEOR) space. Network with HEOR expert stakeholders, global thought leaders, and your peers to explore the importance of scientific evidence in understanding and improving the health and well-being of people across the globe.

Session highlights include high-profile plenary sessions tied to the conference theme "Generating Evidence Toward Health and Well-Being" led by program committee co-chairs, offering insightful commentary on the pressing issues in healthcare today.

Join us for these Plenary sessions…

Monday, 18 November | 8:30 CET

The Evidence-Price Conundrum: What Is the Way Forward for Patient Access?

Moderator: **Yannis Natsis, MA**, European Social Insurance Platform, Belgium

Tuesday, 19 November | 8:30 CET

Ready, Set, Go: The Last Sprint for the EU HTAR

Moderator: **Anne Willemsen, MSc**, Dutch National Healthcare Institute, The Netherlands

Wednesday, 20 November | 11:30 CET

Reality Check: Are We Bridging the Evidence Gaps for Patients?

Moderator: **Patrice Verpillat, MD, MPH, PhD**, European Medicines Agency, The Netherlands

Spotlight sessions will highlight timely topics and innovation in HEOR…

Fit-for-Purpose Real-World Data: Principles and Developments

HEOR in the Era of Generative AI: Navigating the New Frontiers

The Dawn of a New Era: Cross-Border Collaborations—Regional, Pan-European, and Transcontinental—How Will They Shape the Future of Access?

View a snapshot of our in-person short courses scheduled for 17 November…

Advanced Patient-Reported Outcomes

Artificial Intelligence-Powered HEOR: Advancing Insights and Decisions With Large Language Models

Introduction to Applied Generative Artificial Intelligence for HEOR

View all in-person short courses here

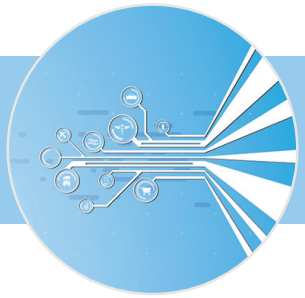
Claim your conference badge and consider adding the Digital Conference Pass to your registration for on-demand viewing from 4 December until 8 January 2025. Details here.

- More at www.ispor.org/Europe2024 and REGISTER TODAY!
- Remember to book your hotel
- Join the conversation on social media using #ISPOREurope

ISPOR Conferences and Events

ISPOR Real-World Evidence Summit 2024 | 17 November

Barcelona International Convention Center, Barcelona, Spain



A co-located event of ISPOR Europe 2024

The ISPOR Real-World Evidence Summit 2024 takes a deep dive into the latest developments in real-world evidence. Global experts will cover the latest findings in the use of real-world evidence across the regulatory/health technology assessment/payer decision-making continuum with a focus on methods, data transportability, and infrastructure. Stay at the forefront of healthcare innovation and policy—view the program and register here.

Enrich your Summit experience by starting your morning with in-person short courses focused on real-world evidence:

17 November | 8:00 – 12:00 CET
Causal Inference and Causal Estimands from Target Trial Emulations Using Evidence from Real-World Observational Studies and Clinical Trials

17 November | 8:00 – 12:00 CET
Developing Decision-Grade Real-World Evidence

17 November | 8:00 – 12:00 CET
Real-World Evidence in External Control Arms: Driving Innovation in Drug Development

ISPOR 2025 | May 13-16

Montreal Convention Centre, Montreal, QC, Canada

Healthcare stakeholders will convene at **ISPOR 2025**, the leading global conference for HEOR, May 13-16 (note new weekday schedule), for discussion and dissemination of the latest trends in healthcare.

Submit your Abstract!

Session and Case Study Abstract Submissions Open:	**October 4**
Session and Case Study Abstract Submissions Close:	**December 13**
Research Abstract Submissions Open:	**November 1**
Research Abstract Submissions Close:	**January 10**

Get in front of your target audience for 2025 – be included in the conference Exhibitor Guide! **Contact sales@ispor.org.**

ISPOR Education

ISPOR Education Center

The **ISPOR Education Center** provides instant access to HEOR education with on-demand programs delivered through a personalized, powerful, and flexible learning platform. Working at their own time and pace, individuals can drive their professional development by growing their knowledge and skills with topical, relevant, and innovative course curricula.

NEW: Multiple Criteria Decision Analysis

At the completion of this online learning module, you will be able to...

- Describe different multiple criteria decision analysis (MCDA) frameworks including ICER, ACC-AHA, ASCO, NCCN, and DrugAbacus.
- Describe MCDA methods such as elementary, V-based measurement mode, simple linear additive model, and linear goal programming models.
- Identify strategies to bridge MCDA and health technology assessment decision making.

View more featured courses, topics covered, and the growing list of courses available at www.ispor.org/EducationCenter

HEOR Learning Lab™

Unlimited, on-demand educational video content

The **HEOR Learning Lab™** provides unlimited high-value content selected from the Society's conferences, summits, and other seminal events. The easily searchable content is focused on the most topical themes impacting the field, including real-world evidence, patient-centered research, digital health, artificial intelligence and machine learning, health technology assessment, economic methods, healthcare financing, access and policy, learning healthcare systems, and much more. More than 550 on-demand sessions are currently available on the platform!

The following are examples of popular sessions available for viewing today:

- **Artificial Intelligence to Support Health Technology Assessment (HTA) and Conducting HTA for Artificial Intelligence Technologies: Recent Developments and Reflections**
- **Assessing Real-World Data From Electronic Health Records for HTA**
- **Generalized Cost Effectiveness Analysis: From Theory to Practice**

Visit the HEOR Learning Lab at www.ispor.org/LearningLabWelcome

ISPOR Education

ISPOR Short Courses

Upcoming ISPOR Short Courses include:

October 16-17 | 10:00AM – 12:00PM EST
(Virtual | Course runs 2 consecutive days, 2 hours per day)

Applying Real-World Data and Novel Data Sources to Advance Patient-Centric Health Equity, Outcomes, and Economic Evaluations

After completing this course, participants will be able to...

- Gain insights on novel data sources, such as consumer data.
- Learn how to integrate this data with additional data sources, including clinical or medical claims data.
- Explore case studies of how this comprehensive, patient-centered data accelerates epidemiology research, patient journey analytics, and clinical trial design.

December 3 | 11:00AM - 12:00PM EST
(Virtual)

Primer on a 6-Step Approach to Budget Impact Analysis

After completing this course, participants will be able to...

- Understand the 6 steps needed to complete a budget impact analysis.
- Distinguish between static and dynamic budget impact models.

December 4-5 | 11:00AM – 1:00PM EST
(Virtual | Course runs 2 consecutive days, 2 hours per day)

Budget Impact Analysis II: Applications and Design Issues

After completing this course, participants will be able to...

- Understand and interpret Excel-based static and dynamic budget impact analyses (BIA).
- Modify existing static and dynamic BIAs based on new evidence or needs.
- Identify good practices for developing BIAs in Excel.

View all in-person short courses at ISPOR Europe 2024 here

Learn more about the ISPOR Short Course Program here

ISPOR Education

ISPOR Webinars

Upcoming webinars include:

October 9 | 10:00AM – 11:00AM EDT

Conducting Research and Survey Studies in Hard-to-Reach Populations

By participating in this webinar, attendees will...

- Understand the benefits of and barriers to involving hard-to-reach groups in survey and health preference research.
- Learn strategies for engagement of hard-to-reach groups.
- Review case study examples of how hard-to-reach groups have been involved in health preference research and important takeaways in terms of adaptations that can be made to recruitment strategies and survey tasks to improve engagement of hard-to-reach populations.

October 10 | 10:00AM – 11:30AM EDT

Patient Involvement in Value and Health Technology Assessment

By participating in this webinar, attendees will...

- Learn about the patient's role in improving decision making and health outcomes and the benefits of incorporating patient perspectives and experiences in decision making.
- Explore the specific challenges faced during patient involvement to gain a deeper understanding of the complexities involved in integrating patient perspectives and experiences into the health technology assessment (HTA) process.
- Identify strategies to enhance patient involvement using practical insights and strategies for value and HTA agencies, industry stakeholders, patient organizations, and patient-centered research organizations.

October 15 | 6:00PM – 7:00PM EDT

Global Perspective on Inequality Aversion: Methods and Learnings

By participating in this webinar, attendees will...

- Gain foundational knowledge and understanding on inequality aversion in the forms of equity analysis, including distributional cost-effectiveness analysis and equity weighting.
- Become familiarized with method adaptations to elicit inequality aversion in the general population based on lessons learned across 4 country settings: Japan, Australia, United Kingdom, and the United States.
- Understand the implications of findings and recommendations for the use of inequality aversion data in HEOR research and policy making.

October 16 | 10:00AM – 11:00 AM EDT

Evidence Generation for Joint Clinical Assessments: How Can AI Boost Efficiency and Maintain Quality?

By participating in this webinar, attendees will...

- Learn how artificial intelligence (AI) tools can increase the efficiency and turnaround times for systematic literature reviews for joint clinical assessments (JCAs) while maintaining quality.
- Understand the possible challenges and barriers to implementing AI for systematic literature reviews.
- Assess the differences in national perspectives.
- Implement steps that can be taken to ensure appropriate, reliable, and transparent use of AI for preparing systematic literature reviews in the JCA context.

ISPOR Education

ISPOR Webinars

Upcoming webinars continued:

October 22 | 10:00AM – 11:00AM EDT

IRA Part III: Medicare's Maximum Fair Prices for the First 10 Negotiated Drugs and Anticipated Cost Savings

By participating in this webinar, attendees will...

- Compare negotiated prices to net prices and other price benchmarks faced by payers before negotiation.
- Identify approaches to estimating the main sources of savings associated from the first 10 drugs selected for negotiation.
- Discuss the potential role of comparative effectiveness research on the derivation of negotiated prices.

View upcoming and on-demand ISPOR webinars: www.ispor.org/webinars

HEOR NEWS

1 Interpreting the First Round of Maximum Fair Prices Negotiated By Medicare for Drugs (Health Affairs)

A study aimed to estimate how Medicare's 2023 spending on certain drugs at the negotiated "maximum fair price" levels would compare to the actual net spending on these drugs in Part D in 2023. The researchers found that due to the context-dependent nature of the negotiation process under current guidance, estimates of the net financial impact of the first round of negotiations are unlikely to be generalizable to future rounds of the negotiation process. In other words, the researchers concluded that the financial effects of the initial drug price negotiations may not be representative of the impacts in subsequent negotiation rounds, as the process is heavily dependent on the specific context and circumstances involved.
Read more

2 Early Findings From the NHS Type 2 Diabetes Path to Remission Program: A Prospective Evaluation of Real-World Implementation (The Lancet Diabetes & Endocrinology)

The National Health Service's Type 2 Diabetes Path to Remission program is a 12-month behavioral intervention to support weight loss involving an initial 3-month period of total diet replacement. In evaluating the program results between September 1, 2020, and December 31, 2022, researchers found that remission of type 2 diabetes is possible outside of research settings through at-scale service delivery, but the rate of remission achieved is lower and the ascertainment of data is more limited with implementation in the real world than in randomized controlled trial settings.
Read more

3 Tribal Health Officials 'Blinded' by Lack of Data (KFF Health News)

Epidemiologists serving Native American communities, which have some of the nation's most profound health inequities, say they're hobbled by state and federal agencies restricting their access to important data.
Read more

4 Consumer Out-of-Pocket Drug Prices Grew Faster Than Prices Faced by Insurers After Accounting for Rebates, 2007-2020 (Health Affairs)

Looking at combined claims data on branded retail prescription drugs with estimates on rebates to provide new price index measures based on pharmacy prices, negotiated prices (after rebates), and out-of-pocket prices for the commercially insured population during 2007–2020, researchers found that although retail pharmacy prices increased 9.1% annually, negotiated prices grew by a mere 4.3%, which they say highlights the importance of rebates in price measurement.
Read more

5 Embedded Bias: How Race Became Ubiquitous in Medical Decision-Making Tools (STAT)

In the 1990s, the National Institutes of Health began mandating the collection and reporting of racial data in its funded research. This marked a pivotal shift, exposing stark racial disparities in health outcomes through quantifiable data. However, this quantification has also enabled a new generation of researchers to develop algorithms that improperly use race as a health risk factor. These algorithmic misuses can perpetuate and even exacerbate the very racial divides the data collection was intended to address, highlighting the complex and potentially problematic implications of how demographic data are leveraged in the pursuit of medical advancements.
Read more

6 Perceptions of Multi-Cancer Early Detection Tests Among Communities Facing Barriers to Healthcare (Health Affairs Scholar)

Looking at the use of blood-based multi-cancer early detection tests (MCEDs), researchers found barriers and facilitators to their adoption across individual, interpersonal, the healthcare system, and societal levels, including adverse psychological impacts, positive perceptions of MCEDs, information and knowledge about cancer screening, the quality of the patient–provider relationship, a lack of healthcare system trustworthiness, logistical accessibility, patient supports, and financial accessibility.
Read more

7 Forecasting the Impact of Means Restriction on the Suicide Mortality Rate in the Region of the Americas: An Ecological Modeling Study (The Lancet Regional Health-Americas)

In the light of the suicide mortality rate increasing in Region of the Americas, despite decreasing in all other World Health Organization (WHO) regions, researchers sought to estimate the impact of implementing national-level means restriction policies (ie, firearm and pesticide restrictions) on this rate and found national-level restriction policies in areas where at least 40% of suicides could be linked to these means could aid the Region of the Americas in achieving the WHO target of a one-third reduction in the suicide mortality rate by 2030.
Read more

8 Cost-Effectiveness and Health Impact of Screening and Treatment of *Mycobacterium Tuberculosis* Infection Among Formerly Incarcerated Individuals in Brazil: A Markov Modeling Study (The Lancet Global Health)

In investigating the potential health impact and cost-effectiveness of Mycobacterium tuberculosis infection screening and tuberculosis preventive treatment for individuals who were formerly incarcerated in Brazil, researchers found that compared with no intervention, an intervention incorporating tuberculin skin testing and treatment with 3 months of isoniazid and rifapentine would avert 31 (95% uncertainty interval 14–56) lifetime tuberculosis cases and 4.1 (1.4–5.8) lifetime tuberculosis deaths per 1000 individuals and cost $242 per disability-adjusted life-years averted.
Read more

9 Changes in Cannabis Involvement in Emergency Department Visits for Anxiety Disorders After Cannabis Legalization: A Repeated Cross-Sectional Study (The Lancet Regional Health-Americas)

In examining changes in emergency department (ED) visits for anxiety disorders with cannabis involvement in Ontario, over a period that involved medical and nonmedical cannabis legalization, researchers found large relative increases in anxiety disorder ED visits with cannabis involvement, which may reflect increasing anxiety disorder problems from cannabis use, increasing self-medication of anxiety disorders with cannabis use, or both.
Read more

10 SARS-CoV-2 Infections Before, During, and After the Omicron Wave: A 2-Year Indian Community Cohort Study (The Lancet Regional Health-Southeast Asia)

Researchers say integrated reverse transcription polymerase chain reaction and serology revealed significant SARS-CoV-2 infection frequency, highlighting the prevalence of asymptomatic cases among previously infected or vaccinated individuals and underscoring the effectiveness of combining surveillance strategies when monitoring pandemic trends.
Read more

HTA POLICY UPDATE

Section Editors: **Sandra Nestler-Parr, PhD, MPhil, MSc; Ramiro E. Gilardino, MD, MSc**

This issue provides a summary of the recently concluded HTA Policy and Methods Review in Australia. We invite suggestions for relevant topics and guest editorials for future issues. Please contact the *Value & Outcomes Spotlight* editorial office with your suggestions.

Enhancing the HTA Framework in Australia: Recommendations of the HTA Policy and Methods Review

Adam Gordois, BA, MSc, Director, HEOR and Value Demonstration, BioCryst Pharmaceuticals, Leeds, United Kingdom

Health technology assessment (HTA) has a long-standing history in Australia. As one of the first countries to implement HTA processes for new medicines, it has been mandatory since 1993 for sponsors to provide an economic evaluation in submissions to the Pharmaceutical Benefits Advisory Committee (PBAC), the independent statutory body advising the Government on drug reimbursement decisions.

The recently completed HTA Policy and Methods Review ("the Review") marks the first independent review of Australia's HTA system in nearly 30 years. It was initiated in October 2022 as part of the current 5-year Strategic Agreement between Medicines Australia (the national research-based pharmaceutical industry association) and the Federal Government. The Agreement recognized the shared goals of: (a) reducing the time for Australians to access new health technologies and (b) maintaining the attractiveness of Australia as a first-launch country by ensuring its HTA processes keep pace with advances in health technology and minimize barriers to access.

The Review's terms of reference covered HTA policy and methods and funding and approval pathways, for medicines, vaccines, highly specialized therapies (eg, cell and gene therapies), other linked health technologies (eg, pathology tests), and foreseeable changes in healthcare. The goal was to develop a comprehensive set of recommendations to Government that are implementable and sustainable; give all Australians equitable, timely, safe and affordable access to high-quality medicines; adopt a person-centered approach to HTA; and ensure HTA policy and methods are suitable for emerging technologies.

An extensive and detailed consultation process to inform the Review—open to all stakeholders—generated 253 submissions across 2 public consultations, "deep-dive" discussions with 116 participants, 1 in-person and 3 online workshops, and 7 commissioned research papers from expert HTA groups. Importantly, the Review was also informed by a rigorous comparative analysis of international HTA systems.

The final report, published September 10, 2024, provides 50 detailed recommendations across a wide range of areas, including improving access to new health technologies, tackling inequity, and making HTA processes simpler for consumer and clinician participation. The recommendations broadly fall into 7 categories—a nonexhaustive summary is provided below.

1. **Create more equitable access for First Nations people and pediatrics**
2. **Streamline pathways for more timely access**
   - Reform HTA and funding processes to be fit-for-purpose, unified, and consistent.
   - Improve reimbursement pathways (eg, streamline cost-minimization submissions, more support for medicines with added therapeutic value, consider alternative modeling approaches).
   - Restructure the vaccines application pathway.
   - Improve the time to access life-saving drugs for ultra-rare diseases.
   - Create performance targets to measure the impact of HTA reforms, jointly owned by government and industry.
3. **Develop policies, methods, and processes to translate HTA recommendations into patient access**
   - Design a framework that supports different funding mechanisms for high-cost/high-impact health technologies.
   - Improve the clarity of post-HTA negotiations.
   - Periodically review reimbursed technologies.
   - Develop practical approaches to manage uncertainty (eg, revised framework for managed entry agreements, bridging fund to facilitate earlier access to therapies of high therapeutic value).
   - Incentivize the development of technologies addressing antimicrobial resistance.
4. **Improve transparency and stakeholder involvement**
   - Improve the transparency and communication of HTA pathways, processes, and decisions (eg, plain language summaries, website improvements).
   - Ensure wider stakeholder involvement in HTA by developing an engagement framework, offering support to consumers and requesting information from sponsors on engagements.
   - Develop an explicit "qualitative values" framework for HTA committees.
5. **Enhance real-world evidence for HTA**
   - Develop a framework to ensure timely access to data, an effective data infrastructure, cross-jurisdictional data sharing, and best-practice methods for data standardization and analysis.

6. Implement methods for confident decision making

- Create a framework to govern how PICO scoping and engagement can support HTA.
- Update guidance on integrating consumer input into HTA processes.
- Develop guidance to assess nonrandomized and observational evidence, surrogate end points, and therapies targeting biomarkers.
- Recommendations for economic evaluation (eg, discount rate reductions for some technologies, comparator selection).

7. Support HTA architecture

- Develop processes to identify areas of high unmet clinical need and bring forward submissions of technologies addressing these areas.
- Establish a national horizon scanning function to improve stakeholder engagement.

To deliver these recommendations, the Review supports developing the capacity and capability of the HTA system and establishing mechanisms for further reviews. The Review reference committee believes that implementing these recommendations will substantially reduce medicine approval times, provide more timely and equitable access to new treatments, and enable greater involvement of those impacted by HTA decisions.

Making the Impact of HEOR Loud and Clear

By Christiane Truelove

When it comes to the effects health economics and outcomes research (HEOR) has on the world of healthcare, the results are often getting lost in the "real world." ISPOR has continued its multiyear initiative, AMPLIFY HEOR, to highlight "the impact of HEOR" through case studies and stories. Although many studies have generated evidence showing how HEOR can be used to improve health and how healthcare is delivered, outside of the HEOR bubble, it's difficult to connect how that information can influence and shape health policy. Ultimately, scientists need to become better communicators about what they do, how they do it, what impact it has outside of their specialties, and why non-HEOR experts should care.

Recognizing a problem, finding a solution, and communicating it broadly: Smoothing the impact of cost sharing in the US Medicare Part D program

Jalpa Doshi, PhD, Leon Hess professor of Internal Medicine at the Perelman School of Medicine, director of Value Based Insurance Design Initiatives at the Center for Health Incentives and Behavioral Economics, and director of the Economic Evaluations Unit of the Center for Evidence-Based Practice at the University of Pennsylvania in Philadelphia, has focused her research program on applying rigorous HEOR and policy methods to identify evidence-based approaches to promote equitable access and appropriate utilization of high-value medications. One of the key areas her research team has contributed to is fixing Medicare Part D cost-sharing policy to enhance access to specialty drug treatments.

> "I quickly noticed that given ongoing trends, the remaining issues with the Part D cost-sharing design were going to generate major access issues for those needing specialty drugs."
>
> – Jalpa Doshi, PhD

"The need to address the issue of improving access to medications came to my attention more than 20 years ago, when I was working on research that ultimately supported the creation of the Part D drug benefit under the Medicare Modernization Act of 2003," Doshi explains. "While that was very exciting to see at an early stage in my career, it was apparent to me that there was going to be a lot more work to be done to get things right. And why was that? Because the cost-sharing requirements under the Part D benefit were so poorly designed that they would continue to result in medication access barriers and disparities for many beneficiaries."

Her team's early work on Part D, after its implementation in 2006, focused on traditional drugs like most other researchers. Initially, the Part D coverage gap (also known as the "donut hole") issue got the most attention. Congress responded and planned to phase out the coverage gap through the passage of the Affordable Care Act in 2010. "While the donut hole fix was welcome news, I quickly noticed that given ongoing trends, the remaining issues with the Part D cost-sharing design were going to generate major access issues for those needing specialty drugs," Doshi says. The number of specialty drug treatments offering advances over traditional drugs was increasing rapidly across multiple disease areas, and many of these novel drug treatments cost tens of thousands of dollars per year. Even after the donut hole fix, the Part D cost-sharing structure required patients to pay a high coinsurance rate ranging from 25% to 33% of the specialty drug's cost. Additionally, there was no annual out-of-pocket maximum, and patients had to continue paying a 5% coinsurance in the catastrophic coverage phase. Given the large racial and ethnic disparities in the income and assets of Medicare beneficiaries, the very high out-of-pocket costs for specialty drugs under Part D were likely going to exacerbate the inequities in access that already existed," Doshi says. "It was a perfect storm in the making, but not really on the radar of policy makers."

In response, starting around 2011, she pivoted her entire team's research into the specialty drug area. Activities were in 4 areas: (1) highlighting the problem; (2) showing the negative consequences associated with the problem; (3) proposing policy solutions on how to fix these cost-sharing issues; and (4) disseminating this work to reach the audiences that could make a difference. Doshi and her team's work highlighted that the existing Part D cost-sharing structure resulted in specialty drug users spending thousands of dollars out-of-pocket each year. Additionally, these out-of-pocket costs were typically "front loaded" at the beginning of the calendar year. "We illustrated that even if an annual out-of-pocket maximum of $2000 was put into place, the 25% coinsurance requirement would result in a Medicare beneficiary having to pay the entire $2000 as a lump sum in January alone if they were using an expensive specialty drug," she says.

Most Medicare beneficiaries could not afford such high costs, which Doshi and her team demonstrated using real-world Medicare claims data. Her team published multiple papers to show the negative consequences of specialty drug cost-sharing burden—high rates of prescription drug abandonment, delays in treatment initiation, nonadherence, and early discontinuation of specialty drug treatments.

> "Specialty drug users were simply being asked to pay too much, too soon during the year and our idea of combining an annual Part D out-of-pocket cap with smoothing offered an actionable policy solution to this problem."
>
> – Jalpa Doshi, PhD

In 2016, her team proposed a novel solution to addressing this problem: an annual Part D out-of-pocket cap *combined* with monthly caps to distribute these costs more evenly throughout the year (also known as "smoothing"). With smoothing in place, and an annual out-of-pocket cap of $2000, patients would be able to spread out what was owed in January over the entire year, essentially requiring patients to pay just about $167 per month. "Specialty drug users were simply being asked to pay too much, too soon during the year and our idea of combining an annual Part D out-of-pocket cap with smoothing offered an actionable policy solution to this problem," Doshi says.

Next, Doshi wanted to move this information from the traditional academic publications and scientific conferences to the stakeholders who could really make a difference. Her team pursued multiple dissemination strategies, including participating in the 2016 and 2017 Patient Access Network (PAN) Foundation Challenge, national competitions in partnership with the *American Journal of Managed Care* asking researchers to submit papers demonstrating the adverse impact of cost sharing and proposing policy solutions. "We participated in these competitions, won awards, but most importantly, we had the opportunity to present our policy solution in front of an audience that included patient advocacy groups, policy makers, and other stakeholders," Doshi says.

> "I think one of our biggest problems is that we are still not able to use simple language to bring "[the impact of HEOR] to life."
>
> – Jens Grueger, PhD

Soon after, several advocacy groups adopted her team's policy recommendations as part of their formal advocacy position. Over the next few years, she and team members developed more digestible communications for policy audiences, such as blogs and commentaries, participated in interviews on panels such as The Hill's healthcare event, and partnered with the PAN Foundation to create an infographic that was widely used in advocacy efforts and shared with Congressional staffers and in written testimony. Eventually, the Inflation Reduction Act of 2022 incorporated her team's idea with provisions for an annual out-of-pocket maximum combined with an option for smoothing via monthly payments under Medicare Part D, both of which will go into effect starting January 1, 2025. These changes will help approximately 3.5 million Medicare beneficiaries and millions more in the future with novel high-cost drug treatments rapidly entering the market in nearly all disease areas.

Communicating value means being concrete

Doshi and her team's strategy and efforts in communicating their findings is a good example of what HEOR scientists can do in order to maximize the real-world impact of their work. But not every research team is able to proactively engage advocacy groups to channel their research and influence policy. This is where ISPOR members' efforts continue to be instrumental in shaping the conversation about the impact of HEOR, says Jens Grueger, PhD, Boston Consulting Group's senior expert for pricing and market access in healthcare based in Zurich, Switzerland. "When you speak to people, they view ISPOR as a scientific platform where we talk about HEOR, recognizing that there are certain things that we need to discuss here: What are the standards for HEOR? How do we use it to improve decision making? For this, we have to bring forward new concepts, which is something that ISPOR has been extremely successful in doing."

"For example, many see ISPOR's Value Flower as a brand, in some ways," Grueger says. The "value flower" reaches beyond health gains and financial gains to shape discussions about health equity, environmental sustainability, and resilience of healthcare systems. "I think that's a very important piece that we are seeing."

But HEOR experts need to go beyond discussions about technical competencies. "We need a broader perspective," Grueger says. "It's not just about the technology, it's about how we provide more equitable healthcare. It's about how we organize things and take that broader perspective— then the technology becomes just an element of that."

A larger issue that persists is how HEOR scientists communicate about what they do and why it is important. "I think one of our biggest problems is that we are still not able to use simple language to bring it to life," Grueger says.

When Grueger's two daughters were growing up, he often found himself having to explain to their friends what he did as a health economist in the pharma industry, and the factors behind drug pricing decisions. "I had to explain to these school children what is the value framework people use in evaluating medical treatment and use very simple language. Several minutes later, they said, 'That's a very interesting perspective. Now I understand that it's not about profits. It's about the evidence that you are producing; it's about the value that is associated with these outcomes that you're producing; and the prices are a consequence of that.' It made them realize that these decisions aren't simply pulled from thin air.'"

> "We need to focus more on that communication piece–not only from our leaders in HEOR, but also begin training our young colleagues to recognize that communication is an important piece for what they're doing."
>
> – Jens Grueger, PhD

Grueger has also had to conduct communication courses for senior managers in pharma on health economics, pricing, and profitability. "When you have a microphone in front of you and then CNN asks you, 'So what about the price for this new medicine?' That's when people tend to freeze and try to pivot to a different topic." Grueger says. "We need to focus more on that communication piece—not only from our leaders in HEOR, but also begin training our young colleagues to recognize

that communication—that is, translating and synthesizing the key results of their research—is an important piece for what they're doing."

"It's not that it's easy to do, but you get more confident as you practice these things. We practice building models; we practice doing scientific proofs. We also have to practice our communication."

In his career as a health economist, Darius Lakdawalla, PhD, director of research at the USC Schaeffer Center for Health Policy & Economics in Los Angeles, California, is familiar with the struggle of communicating the value of products. Too often, people who complain about the cost of a drug dismiss the innovation incentive. "There seems to be a resistance to that economic idea when it comes to paying the price for the therapies we have today," Lakdawalla says. "This is an issue that cuts across all types of high-cost drugs. Take, for example, innovative treatments for hepatitis C, that were brought to market in 2013. Even though these new drugs replace regimens that cost a lot of money on a lifetime basis, people were hung up on the $1000 sticker price of each pill. I put it in these terms with one reporter: If there were one pill that would cure your disease but it costs more than $80,000 for the pill, would you pay it? The point is that it doesn't make sense to complain about the unit prices of the things just because they're cheap to produce when it's ultimately about value."

> "It doesn't make sense to complain about the unit prices of the things just because they're cheap to produce when it's ultimately about value."
>
> – Darius Lakdawalla, PhD

He admits that explaining value still remains a problem. "It helps to make things more concrete, which is something we've tried to do. For instance, when you pay for innovation, it's not just that you get more innovation. It's that you extend human life and you make lives better. Putting it in these terms helps, but it doesn't completely bridge the gap. There will still be people who say, 'if these things are so cheap to produce, why should we pay so much for them?'"

To get to the other side of these cost vs value arguments, health economists and HEOR experts must be able to succinctly sum up their work. Recently, Lakdawalla and colleagues at USC Schaeffer produced a paper showing Medicare coverage of drugs for treating obesity could significantly reduce costs. They calculated that coverage for new obesity treatments could generate approximately $175 billion in cost offsets to Medicare in the first 10 years alone, and by 30 years, cost offsets to Medicare would increase to $700 billion. And in an earlier paper on pricing, Lakdawalla and colleagues explained that if the United States instituted European-style drug pricing measures, Americans would lose more than half a year of longevity, which is about the same as what would happen if every cardiac surgeon in America suddenly forgot how to perform bypass surgery, he says. "Now that kind of analysis resonates more with people than just talking about elasticities and this innovation effect and that change in the number of drugs launched, that's all too theoretical. It has to be made as concrete as possible."

> "Does the rate of return on the investment make sense or not?"
>
> – Darius Lakdawalla, PhD

In the end, investment in health innovation has to be examined like any other investment, whether it's building bridges and airports or investing in microchip manufacturing factories. "It's all in the question of whether it's worth it to invest in these things or not," Lakdawalla says. "The way that I would look at it is: Does the rate of return on the investment make sense or not?"

HEOR experts and health economists should be paying attention to what patients care about, which is important for several reasons, Lakdawalla says. "It shows us when our theories are wrong. If we're really paying attention to what patients are doing and the theory is inconsistent with what patients are doing, then it's wrong and needs to be fixed. But it's also about how you communicate the work. If you are paying attention to what patients care about, then you ought to be communicating the work in the terms that patients care about. I think that we should always be communicating in terms of outcomes that ordinary people—people who are not academics—care about. And that message has to be framed in a way that people can readily understand."

While people have to be made to care about innovation incentives, they don't have to be made to care about their life expectancy, their health, or their kids' probability of surviving into adulthood. "These are all obvious human values. And the more we can be communicating our findings in terms of those human values, the easier it's going to be to have an impact on decisions outside of our little world," Lakdawalla says.

Christiane Truelove is a healthcare and medical freelance writer.

By the Numbers: HEOR Innovation and Impact

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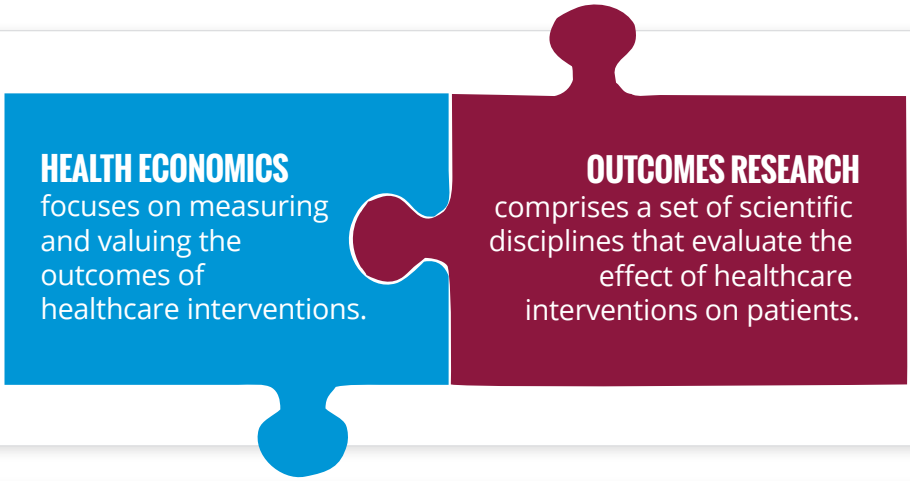
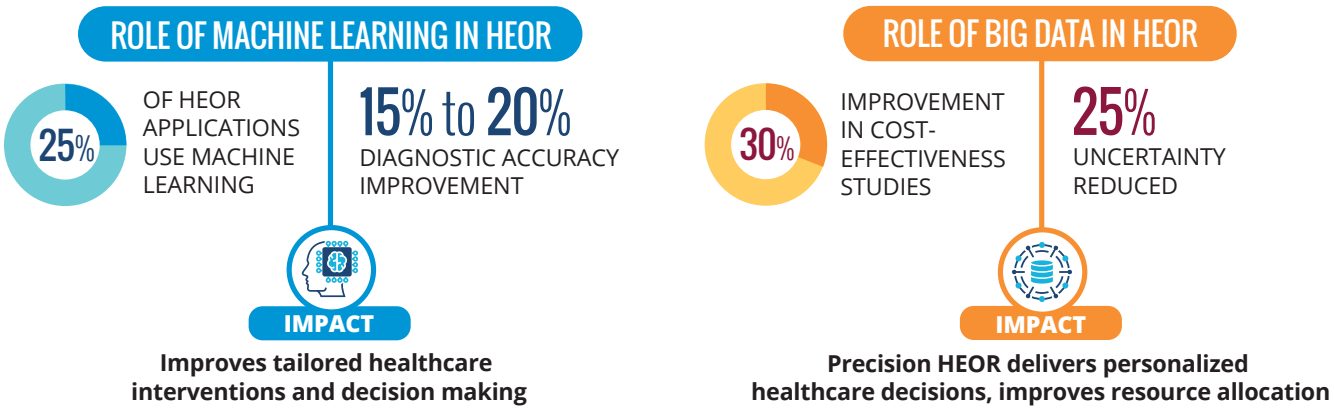
HEOR Explained

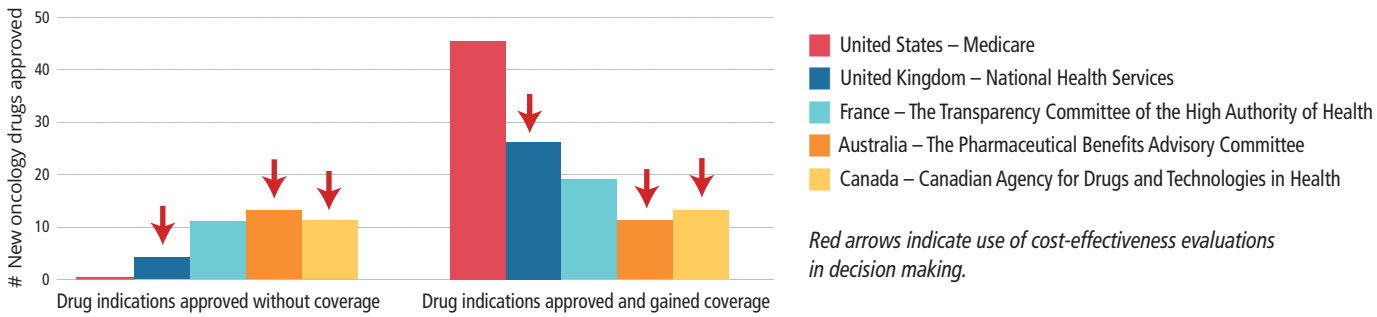
HEOR is the confluence of 2 fields that work together to provide powerful data and insights for healthcare decision makers.



The Role of Machine Learning and Big Data in Amplifying HEOR's Impact



Coverage Decisions of New Oncology Drugs between 2009 to 2013



Red arrows indicate use of cost-effectiveness evaluations in decision making.

Big Pharma Says, "Thanks, but No Thanks" to Its Own HEOR Groups

Scott D. Ramsey, MD, PhD, Curta, Inc, Fred Hutchinson Cancer Center, University of Washington, Seattle, WA, USA

Many large pharmaceutical companies have restructured HEOR by eliminating standalone teams and moving associates to Medical Affairs or Market Access.

The decision to restructure HEOR raises important questions about the value and future of HEOR within the industry.

There is still a need for HEOR evidence that is pragmatic, clinically integrated, and generated quickly.

Last spring, I had a wonderful time at the 2024 annual ISPOR conference in Atlanta, Georgia. I attended some fantastic sessions and caught up with many friends and colleagues. Overall, the vibe was very positive. Still, there was a darker undertone that was palpable: several very large pharmaceutical firms had substantially reorganized or eliminated their health economics and outcomes research (HEOR) groups. The story was remarkably similar for each of them: the HEOR leads were sacked and the midlevel employees were sent to other groups—most often Medical Affairs or Market Access.

Is HEOR losing clout in pharma?

So many things played through my mind as I heard these remarkably similar stories. Honestly, my first thought was how harsh the corporate world can be. Unlike my familiar world of academics, individual performance on the job is a second-order issue relative to the bottom line of corporate revenues. But this leads to another question: If a big company is facing tough times, how does it decide what is fat versus muscle? One person confided that they were pretty sure that the senior leadership simply drew a line, with those above the salary limit removed and those below kept (and scattered). If true, I think that Lester Thurow's quote about bad business decisions might apply here:

"If a group of people has no sense where they came from, it is difficult for them to have a sense where they should go."

One stream of thinking is that all this is much ado about nothing. Corporate restructuring is as regular as the seasons in big pharma. How would the sharp minds at McKinsey and Deloitte keep their very large salaries if they didn't come up with ever better ways for companies to keep their edge? I am also mindful that the pharmaceutical industry, for all its weight and profit, is a tough industry. Many companies that initiated the layoffs had a number of pipeline drug failures, particularly in oncology, a space that I know well.

Moving beyond the ways that pharma adapts its business to product successes and failures, what does this all mean for those of us in HEOR? The obvious first question: Is HEOR losing clout in pharma? Certainly, HEOR groups in the United States face headwinds that are not issues in the rest of developed world. The US government has been unwelcoming to cost-effectiveness analysis, and most commercial insurers have not found a way for cost-effectiveness analysis to work in their business models. Of course, cost-effectiveness is only one component of HEOR's purview. Could it be that all the other work they do has also been devalued? More on that in a moment.

Are those of us who work in this space producing the type of information that companies need to support their products?

A second related question came to mind: Maybe pharma doesn't see a need to have separate HEOR groups? HEOR operates in a somewhat uncomfortable space in these companies. It is a science-based discipline but a hybrid of many fields of study: epidemiology, economics, modeling, patient reported outcomes, etc. The audience for HEOR-oriented studies is very broad and, perhaps for that reason, it doesn't fit very well into typical pharma org charts. While there is a clear regulatory role for HEOR outside of the United States (ie, for health technology assessment) *inside* the United States, HEOR has no regulatory underpinnings and therefore ends up being used in other ways to bolster messages of comparative effectiveness, budget impact, and (yes) value compared to competitors. As such, HEOR studies can be particularly influential for products that face a lot of competition. And here is one reason why

I found the pattern of the layoffs to be so strange: it takes years to build up the skills and experience that are needed to navigate HEOR. People who are at the top of this pyramid are very rare indeed. I think it will take years for pharma to realize that letting go of their most senior HEOR leaders was a grave mistake.

The HEOR work isn't going away.

My third question was more self-reflective: Are those of us who work in this space producing the type of information that companies need to support their products? Certainly, the public self-criticism that plagues our field is not helpful (eg, QALY-bashing). In my opinion, we also tend to add complexity instead of thinking how we could make a decision task easier, at least from the point of view of people who might want to use our work to make decisions. These issues don't take away the fact that decision making is hard in medicine, with multiple attributes that must be weighed simultaneously. What we do—collect, synthesize, and summarize vast amounts of information into common, accepted frameworks—should not be discounted. Otherwise, it comes down to who can shout the loudest.

Will moving HEOR groups into Medical Affairs and Market Access change the field? While the essential products that HEOR provides may not change, the culture that our HEOR colleagues in pharma work in will.* My sense is that the speed of decision making in Medical Affairs and Market Access is *much* faster than most HEOR professionals are used to. Pharma's HEOR teams and the large consultancy industry that supports them may need to live with a few more rough edges on their products and maybe a little less time asleep in their beds. In addition, US pharma is oriented to *customers*, not populations. Tailoring our work to address the tastes and preferences of pharma's many customers will take some rethinking (*hint*: they won't ask for more ways to characterize uncertainty). My personal expectation is that the winning formula will orient towards simpler, more clinically oriented models that place less emphasis on applying value weights to the endpoints.

Finally, here is one critical point that I took away from my discussions with persons who were impacted by the layoffs: *the HEOR work isn't going away*. While it is too soon to tell (it takes months for organizations to "recover" from reorgs and downsizing), nobody I spoke with said that their projects were being eliminated. Also, when I look at the macro trends, it also doesn't feel like HEOR is going into retreat any time soon. High-cost, low-value medicine hasn't disappeared, nor have the healthcare cost pressures facing individual patients, businesses, and governments. Providers and insurers will still try to ferret out what isn't necessary and do what they can to mitigate the cost burden of what is necessary in healthcare. As long as the organizations that pay for these products ask for the information that HEOR provides, pharma will be obliged to supply it.

HEOR is dead. Long live HEOR!

Note: A previous version of this article was first published in the June 2024 issue of Curta on Call*, a quarterly blog from Curta's Chief Medical Officer on current topics, trends, and issues in health economics and outcomes research.*

* HEOR is likely to change more for US-based groups versus those outside the United States.

A New Frontier in Health Economics and Outcomes Research: Generalizing Clinical Trial Outcomes to Real-World Settings

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Real-world evidence of effectiveness is vital to decisions about access and pricing, but regulatory approval still relies mainly on clinical data in controlled settings.

Bayesian and machine-learning methods can help bridge this gap by allowing analysts to reliably infer real-world effectiveness from clinical trial and real-world data.

Predictions of real-world outcomes should characterize not just a single average outcome but the full probability distribution of possible outcomes, along with an accurate assessment of how much uncertainty surrounds the predictions.

These approaches can be particularly helpful in rare disease cases and other contexts where trial and real-world sample sizes are small.

Introduction

For new medicines, and even many established ones, evidence of effectiveness rests primarily on data from a pivotal clinical trial designed for regulatory approval. Yet, in nearly all cases, clinical trial participants differ significantly from real-world patients who use the drug. This issue came into sharp relief over the past few years as novel treatments for Alzheimer's disease emerged.

In 2021, the US Food and Drug Administration (FDA) approved aducanumab, the first therapy targeting the fundamental pathophysiology of the disease. Aducanumab was the first Alzheimer's drug approved by the FDA in almost 2 decades; and its approval reflected the dire need of patients suffering from Alzheimer's disease. Indeed, the FDA approved aducanumab through its accelerated approval pathway that emphasizes surrogate endpoints—in this case, positron emission tomography imaging showing that it reduced amyloid beta plaque accumulating in the brain.[1]

The Centers for Medicare & Medicaid Services (CMS), which runs the Medicare program, was not as sanguine about aducanumab's efficacy in their population.[2] CMS also fretted about the potential cost. Indeed, CMS announced that 2022 premiums in Part B—the program responsible for paying for aducanumab—would reflect the largest premium increases ever.[3] Given these cost and efficacy concerns, CMS proposed a novel evidence development policy[4]—only Medicare patients enrolled in randomized clinical trials would be eligible for coverage. In effect, Medicare was mandating additional clinical trials, for their covered population, after FDA approval.

The policy seemed misguided. For example, if randomization is blinded, it meant that Medicare beneficiaries assigned to placebo might still have to pay out-of-pocket costs. In the wake of patient uproar, CMS ultimately relaxed their policy for all drugs in this space. Rather than relying on randomized clinical trials, CMS now requires treated patients to be part of clinical registries as a condition for coverage. In effect, CMS chose to "support the collection of real-world information to study the usefulness of these drugs for people with Medicare."[5]

For new medicines, evidence of effectiveness rests primarily on data from a pivotal clinical trial designed for regulatory approval. Yet, in nearly all cases, clinical trial participants differ significantly from real-world patients who use the drug.

This conundrum plays out in many countries, patient populations, and therapeutic areas. Manufacturers must support their pricing based on real-world effectiveness, payers must make reimbursement and access determinations, and clinicians and patients must make treatment decisions. The challenges are further magnified in rare disease treatments, where trials may involve relatively few patients.

Fortunately, credible and rigorous methods exist for generalizing health outcomes to real-world populations of interest. They remain underused and underappreciated in comparative effectiveness research, perhaps due to their complexity. In this article, we describe these methods and offer a path to more reliable estimates of comparative effectiveness, even in rare diseases with

Table: Common probability distributions for probabilistic models

Data type of outcome	Example distributions
Continuous data	Normal, Student's, skew-normal, logistic, Gumbel
Categorical data	Bernoulli, categorical, binomial, multinomial
Survival data	Exponential, Weibull, Gompertz, gamma, log-logistic, lognormal, piecewise exponential
Count data	Poisson, negative-binomial

small sample sizes. We illustrate our findings with an application to Duchenne muscular dystrophy (DMD) gene therapy.

Probabilities, not averages

When predicting real-world outcomes, a common pitfall is to focus on average health outcomes. This may seem attractive since clinical trials typically read out mean (or median) outcomes. However, focusing on averages hides information pertinent to decision makers. Empirical research demonstrates that patients themselves care about more than just average outcomes; they may value treatments that reduce their risk[6] or treatments that increase the chance of a substantial gain, even when the mean improvement is relatively limited.[7,8] (These findings reveal complex patient preferences for health risk that are captured in Generalized Risk-Adjusted Cost-Effectiveness, or GRACE).[9-13] For clinical decision makers, average outcomes can conceal benefits to particular subpopulations.[14] For policy makers, average outcomes shed no light on how new treatments affect societal inequality. Finally, payers and self-insured employers may wish to understand the risks of incurring above-average costs or deriving below-average clinical benefits.

All these stakeholders are better served by using *probabilistic* models, which predict entire probability distributions rather than a narrow summary like the average.[15] Examples of probability distributions for common types of outcomes are shown in the **Table**. As discussed below, Bayesian statistical models are particularly attractive because they are inherently probabilistic and quantify multiple sources of uncertainty.

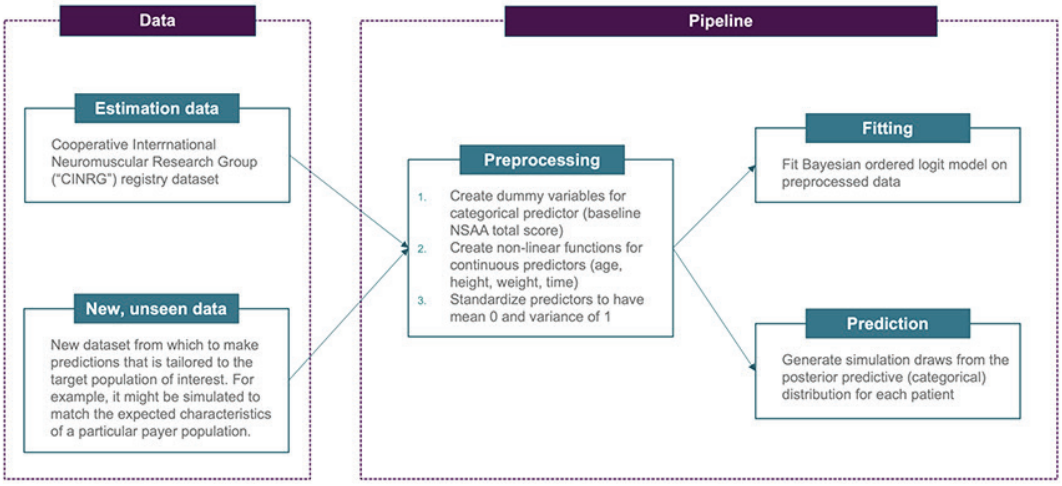
To illustrate the practical estimation of probabilistic models, we studied disease progression in patients with DMD using the North Star Ambulatory Assessment (NSAA) total score, which reflects patient performance on 17 tasks to measure functional motor ability.[i] We measured losses in total score from baseline and reported them in 4 categories (0, 1-2, 3-5, and 6+). We then predicted the distribution of losses in total score from baseline.

Learning from machine learning

It is often not obvious what model(s) or variables to use when forming predictions. When used properly, machine-learning approaches can inform these decisions by using data to determine which modeling choices result in the best predictions of salient outcomes distributions.[16]

Best practice in machine learning combines all model-building steps into a single automated process known as a *pipeline*,[17] which combines the statistical model relating inputs to outputs with all *preprocessing steps* that prepare the inputs for model fitting. We refer to the full series of steps as a Bayesian model pipeline. Our DMD Bayesian model pipeline is shown in **Figure 1**.

Figure 1: Bayesian model pipeline for modeling changes in the NSAA total score. Four indicator variables were used for the baseline NSAA total score (0-16, 17-23, 24-38, and 29-34), which resulted in roughly balanced proportions among the CINRG population. Five different specifications were used for the continuous predictors and incorporated into model averaging: (1) linear functional form, (2) linear functional form interacted with time, (3) polynomial of degree 2, (4) natural cubic splines with 4 degrees of freedom, and (5) natural cubic splines with 3 degrees of freedom.



CINRG indicates Cooperative International Neuromuscular Research Group, NSAA, North Star Ambulatory Assessment.

A pipeline produces numerous benefits. First, it makes the process of generalizing trial results to multiple target populations more transparent, more efficient, and less error prone. Second, it is well-suited to "Living HTA,"[18] allowing value assessments to be updated in real-time as new data becomes available. Third, evaluations of a model on out-of-sample data are more reliable because the entire modeling process is included in the evaluation.[16] Finally, pipelines ensure greater reliability when predicting outcomes for new populations

[i] Each task is scored from 0 (worst) to 2 (best) so the total score ranges from 0 to 34.

that were not used to fit the model (ie, when performing "out-of-sample" predictions).[16,19] As shown in **Figure 2**, we used a fresh sample of patients with DMD to assess whether out-of-sample predictions matched observed probabilities.

Quantifying multiple sources of uncertainty

Clinical, reimbursement, and pricing decisions are made against a backdrop of uncertainty. For example, the most cost-effective treatment is the one with the highest expected value when considering all sources of uncertainty. Furthermore, both decision makers' confidence in cost-effectiveness analyses results and the value of collecting additional postreimbursement data depend on the probability that a treatment is cost-effective.

> Empirical research demonstrates that patients themselves care about more than just average outcomes.

There are 3 prevalent types of uncertainty in outcomes analysis. *Structural uncertainty* reflects uncertainty about which underlying model structure matches the real world (eg, whether the true model is linear or nonlinear). *Parameter uncertainty* reflects uncertainty about the values of individual model parameters (eg, the values of the regression coefficients or the probability of a successful outcome). *Sampling uncertainty* reflects uncertainty in the distribution of the outcome when measured in a finite population (eg, given a fixed probability of success, the number of patients in a payer population of size N that will succeed).[ii]

Predictions from our DMD model reflect all 3 sources. Multiple Bayesian models with different specifications of the predictors are assigned weights based on out-of-sample performance using Bayesian model averaging[20] techniques (reflecting structural uncertainty).

Posterior draws of the regression coefficients were generated for each model (reflecting parameter uncertainty). Changes in total scores for each patient are then simulated from a categorical distribution using the weighted models (reflecting sampling uncertainty). The predicted proportion of standard of care patients in each functional status category are shown in **Figure 3**.

The optimal use of real-world data

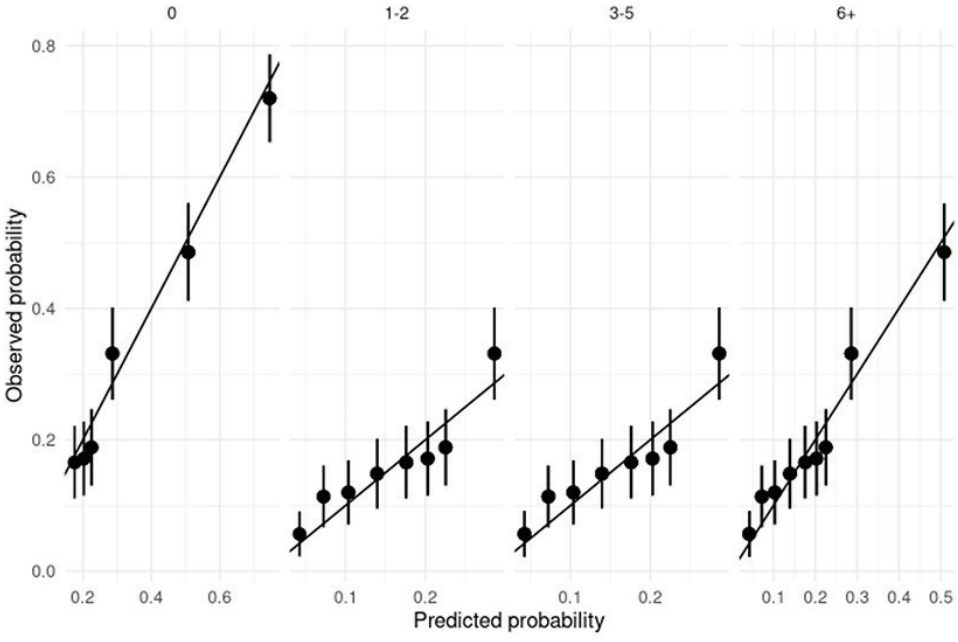
When a drug has not yet been launched, it may seem like real-world data (RWD) would be of little use since these are not available for the drug of interest. In fact, RWD can be quite useful in this context.

Randomized controlled trials (RCTs) are often lauded because they can estimate unbiased *relative* (novel treatment versus standard of care) treatment effects, while nonrandomized RWD studies are criticized for potential selection bias.

These assessments are correct but incomplete. RWD, unlike RCTs, better represent real-world patients and thus better estimate *baseline risk* (ie, outcomes that obtain under a prevailing real-world standard of care). Thus, RCTs are ideal for causal inference, but RWD are best for prediction and external validity. Thankfully, analysts can benefit from the best of both worlds.

Relative treatment effects from RCTs and baseline risk from RWD can be optimally combined to estimate absolute clinical benefit using an approach called *risk magnification*.[21] For instance, the predicted NSAA total scores for standard of care patients with DMD can be combined with an empirically derived odds ratio that reflects the relative treatment effect observed in an RCT. The result is a predicted treatment effect for the new drug that accounts for the characteristics of real-world patients

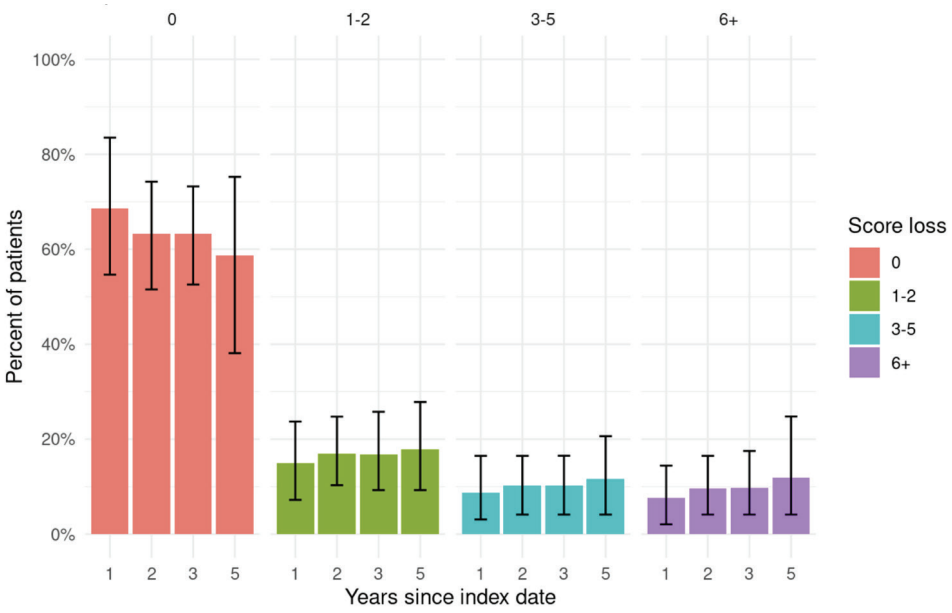
Figure 2: Calibration plot comparing predicted out-of-sample probabilities to observed probabilities. Each column represents a total score loss category. Predictions were stratified into bins based on prediction risk. Mean observed NSAA total score loss probabilities within each bin are shown on the y-axis and predicted NAA score loss probabilities within each bin are shown on the x-axis. A perfect prediction lies along the 45-degree line. Predictions were made using 5-fold cross-validation whereby the entire Bayesian model pipeline was fit on 4/5th of the data and tested on the remaining 1/5th, 5 times.



NSAA indicates North Star Ambulatory Assessment.

[ii] Sampling uncertainty may only be relevant in some contexts. For instance, CEAs should arguably estimate average outcomes in an infinitely large population and therefore eliminate sampling uncertainty. On the other hand, sampling uncertainty is relevant in budget impact analyses because costs accrue among a population of a fixed size (forecasts of costs for rare disease will surely be more uncertain than forecasts of costs in highly prevalent diseases).

Figure 3: Predictions of NSAA total score losses over time among patients treated using the standard of care in the CINRG registry dataset. Error bars are 95% credible intervals. Predictions were generated from posterior predictive draws of the ordered logit model averaged across the competing model specifications. A score loss of 0 occurs if the NSAA total score either improved or was unchanged; positive score losses occur when the NSAA total score declines (disease worsens).



CINRG indicates Cooperative International Neuromuscular Research Group; NSAA, North Star Ambulatory Assessment.

with DMD using the current standard of care. This approach has been favored by statisticians who argue that relative treatment effects are less likely to vary across individuals than baseline risk.[22][iii] Estimation of baseline risk is critical because absolute clinical benefits may vary considerably by baseline risk even if relative treatment effects are constant.

Making the most of limited data

Bayesian models require the analyst to specify "priors," which reflect a priori beliefs about the distribution of parameters. Some criticize this requirement on the grounds that subjectively determined priors can heavily influence model estimates. Yet this criticism overlooks the way in which analysts and decision makers already use priors. "Classical" statistical approaches might subject a set of estimates to a "sanity check" from clinical or other experts and then reject the model if it fails to meet those clinical expectations. This process is itself subjective, arbitrary, and (often) nonreproducible. In contrast, a formal process of specifying priors imposes systematic and structured discipline on what would otherwise be an opaque and ad hoc process. And, priors improve predictive performance by incorporating external or expert views that would ordinarily be held separate from a model-estimation process.

Bayesian priors can be particularly helpful when sample sizes are small. In such cases, models are typically overfit to the available data resulting in poor out-of-sample predictions coupled with overoptimism about predictive performance. We mitigated this problem by using a "shrinkage" prior.[23] Intuitively, the shrinkage prior leverages the result that historical data may mislead because performance above or below an average is likely to suffer regression to the mean.[24] First proposed in the peer-reviewed statistics literature in the 1950s, the shrinkage prior rigorously accounts for this "regression to the mean" problem.[25]

Priors can also help combine disparate datasets or extrapolate to new patient populations. For example, historical clinical trials are often available for the standard of care, but there is a risk that combining them with RWD on standard of care patients will reduce the representativeness of the data. Priors can address this potential loss of representativeness, because the amount by which the RWD "borrows" from the trial data can be weighted by the extent to which *outcomes* in the trial data are like the RWD.[26] Similarly, if there is a need to make predictions in an entirely new population (eg, in children after an initial study in adults), the new study (in children) can borrow from the data from the initial study (in adults), reducing the cost of data collection.[27]

The way forward

Better estimates of real-world value benefit almost all healthcare stakeholders. Coverage decisions by public and private payers will be based on economic analyses that better reflect their population and financial risk. Citizens will benefit from better decision making and more efficient clinical trials. Both payers and manufacturers can better assess their risk in outcomes-based contracts.

> Decision makers' confidence in cost-effectiveness analyses results and the value of collecting additional post-reimbursement data depend on the probability that a treatment is cost-effective.

Unfortunately, the methods needed to generate such benefits are currently underused and underappreciated. One reason is that health economic models are typically divorced from the statistical methods and data used to parameterize them. This is a mistake; economic and statistical modeling should not be thought of as separate exercises, but as essential components of a unified and coherent model applied to predict real-world health outcomes. While statistical

[iii] Effect modifiers (interacting variables) can be introduced if there is evidence that relative treatment effects are heterogeneous.

methods may seem complex, advances in machine learning have taught us how appropriate software can bring complex algorithms to practice.

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Quantifying and Maximizing the Impact of Digital Innovation in Cancer Patient Navigation

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Patient navigation facilitates equitable access to care, reduced financial toxicity, and improved cancer outcomes. However, resource limitations impact health system ability to provide navigation. Digital solutions can help but cost is a primary barrier to investment. With CancerX resources, health systems can forecast return on investment from implementing digital patient navigation.

CancerX resources demonstrate real-world applications of economic modeling and the importance of these efforts to the evidence base for healthcare decision making.

CancerX is a public-private partnership established by The White House Cancer Moonshot and as such, all of the resources produced by the initiative are made freely available to all.

Patient navigation and CancerX: A digital innovation accelerator within the Cancer Moonshot

The high costs and complexities of cancer treatment can exacerbate health disparities, undermine tailored treatment plans, and produce negative health and quality-of-life outcomes for patients. Patient navigation is an effective strategy for supporting patients and their families as they manage the clinical and financial side effects of cancer treatment but is too often unavailable to patients with cancer who may benefit due to health system resource constraints.

To address barriers in access to patient navigation services, The White House Cancer Moonshot, and its associated initiative CancerX, are investing in approaches to make patient navigation scalable and reimbursable. Patient navigation services are a focus of The White House Cancer Moonshot goals and are newly reimbursable under the 2024 Centers for Medicare & Medicaid Services (CMS) payment rule aimed at advancing equitable access to whole-person care.[1,2]

> Patient navigation services are a focus of The White House Cancer Moonshot goals and are newly reimbursable under the 2024 Centers for Medicare & Medicaid Services payment rule aimed at advancing equitable access to whole-person care.

CancerX, a public-private partnership announced by The White House as a national accelerator to boost innovation in the fight against cancer, has also produced health system resources aimed at quantifying and maximizing the return on investment associated with digital patient navigation for health systems. These resources are freely available and demonstrate the capacity of economic modeling to support real-world decision making in the healthcare setting.

The impact of patient navigation on measures that matter to patients and health systems

Patient navigation is a hallmark feature of modern, comprehensive cancer care. Navigation increases access to cancer screening and timely treatment and improves patient satisfaction and quality of life.[3,4] Financial navigation, in particular, is shown to produce significant cost savings for patients, facilitating consistent appointment attendance, treatment plan adherence, access to needed medications, and, ultimately, improved survival outcomes.[5] Navigation also produces health system benefits in the format of reduced resource use and spending on acute care and long-term hospitalizations.[4] However, health systems are often using excess revenues from elsewhere in the budget to provide patient navigation services to patients with cancer who have acute issues, such as trouble getting to their next appointment.

Digital health platforms exist as a potential solution to the scalability and sustainability issues faced by health systems implementing patient navigation. They are effective in standardizing an approach to screening for patient distress. They are also proven to reduce emergency department use and administrative burden for providers and patient navigators, allowing each to work at top-of-license to solve more complex clinical issues.[6] The benefits of digital navigation are documented in published literature but are not yet systematically quantified to support healthcare decision making around investment.

Quantifying the impact of digital patient navigation in cancer

To quantify the health system benefits associated with digital cancer navigation and support health system decision making around investment in digital solutions to scale navigation programming, CancerX has developed

a customizable return-on-investment (ROI) calculator that forecasts the impact of these solutions on patient and health system outcomes. The conceptual framework for the ROI calculator suggests that digital patient navigation solutions that provide financial navigation to patients with cancer drive down rates of patient financial toxicity, thereby improving patient treatment adherence and reducing healthcare need, further reducing healthcare resource use and expenditures.

> CancerX has developed a customizable return on investment (ROI) calculator that forecasts the impact of these solutions on patient and health system outcomes.

The ROI calculator was developed through the collaboration, facilitated by the Digital Medicine Society (DiMe), of 24 CancerX member organizations, including ISPOR members (Chia Jie Tan, Ishfaq Rashid, and Carl Asche) from the University of Utah College of Pharmacy Pharmacotherapy Outcomes Research Center.[7]

The free ROI calculator is designed to be used by stakeholders that purchase or sell digital solutions to support comprehensive cancer patient navigation. In our effort to estimate the ROI generated from the example digital cancer navigation platform we selected, we found a positive return of 114% over 5 years, driven by the capacity of the platform to reduce financial toxicity for patients, thereby reducing rates of medication nonadherence and reducing healthcare resource use on hospitalization and outpatient visits.

Solutions for scaled digital patient navigation in cancer

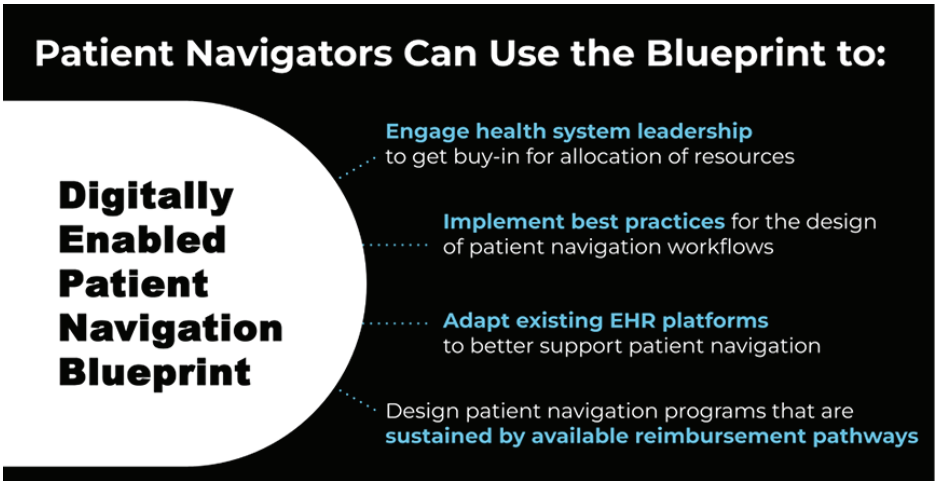
CancerX has also developed free tools to support health systems in maximizing the ROI they generate from investing in the implementation of digital health solutions to support cancer navigation. The CancerX Digitally Enabled Patient Navigation Blueprint is designed to enable cancer patient navigation programming that is standardized, efficient, and reimbursable. It supports business case development for the implementation of digital patient navigation that improves access to care and reduces patient financial toxicity. It provides instruction on how to adapt existing health technology platforms (eg, Epic and Oracle Health) to support patient navigation. It also provides a standardized workflow for digital patient navigation and guidance on how patient navigation divisions should document and bill for their services, ensuring reimbursable, sustainable programming (**Figure 1**).

Conclusions

This work has several implications for health system decision makers within cancer centers. As they evaluate digital solutions for purchase, these decision makers are interested in the ROI that might accrue from investment in digital patient navigation solutions. Patient navigation programs enhance equal access to care, reduce patient financial toxicity, and improve health and quality-of-life outcomes for patients with cancer. However, resource constraints can hinder the widespread implementation of these programs. While digital solutions can help to address resource constraints, unknown total cost and ROI remain primary obstacles to adopting digital health solutions for cancer patient navigation.

Health systems and patients need support establishing and engaging in digital patient navigation programs to ensure efficient, effective, and equitable cancer care. Health system decision makers and cancer care navigators can use these freely available CancerX tools in the design and implementation of digital navigation programming to improve equity and reduce out-of-pocket costs for patients across their cancer journey. A recording of the launch event for these resources supported by the CancerX "Advancing Digital Innovation to Improve Equity and Reduce Financial Toxicity in Cancer Care Research" project can be found at Advancing Equity and Reducing Financial Toxicity in Cancer Care.[7]

Figure 1: Features of the CancerX Digitally Enabled Patient Navigation Blueprint



EHR indicates electronic health record.

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Researcher Difficulties Using Secondary Data Sources to Generate Real-World Evidence: Results From an Online Survey

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The past 4 decades have witnessed an explosion in use of real-world data sources to generate real-world evidence among an expanding array of health system stakeholders.

Despite wider proliferation of real-world data sources and solidification of analytic methods, it remains unclear to what extent these advances have made real-world evidence generation easier.

This survey elicited current data on the state of affairs associated with using real-world data sources to generate real-world evidence.

Introduction

Analyses of secondary data sources, such as billing claims and electronic health records (EHRs), have been a mainstay of health economics and outcomes research (HEOR) for more than forty years. During that time, the field has seen widespread proliferation of real-world data (RWD) sources, technological innovations to enable data linkages, refinements of analytic methods to limit bias and confounding, and articulation of real-world evidence (RWE) use cases by payers, regulators, and other health system stakeholders. An entire RWD/RWE ecosystem has emerged in virtually every country where data on patient encounters with the medical care system are stored electronically. ISPOR and other professional organizations offer training in RWD analytics, and the field of data science has emerged as an academic discipline to enable the next generation of analysts to become credentialed in the latest tools and techniques, including artificial intelligence (AI).

> An entire RWD/RWE ecosystem has emerged in virtually every country where data on patient encounters with the medical care system are stored electronically.

With all these developments, it is an open question as to what extent generation of RWE from secondary RWD sources remains a challenge. Has the expanding array of available and linkable data sources made identifying those that will meet one's research objectives an easier or more daunting task? Have the methodologic advances for analyzing RWD made identifying the study design and selecting the statistical techniques more straightforward or more confusing, requiring greater sophistication to sort through? And with a growing body of literature describing past studies to draw from, is the task of defining computable operational definitions to select study patients, assemble them into comparison groups, track their comorbidities and concomitant medications, and assess treatment outcomes a less painstaking undertaking, or more?

This paper reports results from an online survey that was conducted to gain insights into the degree of difficulty researchers have identifying, evaluating, and analyzing secondary RWD sources to generate RWE.

Survey Design & Implementation

The anonymous online survey was fielded during the period of February to May 2024. The survey first asked researchers for their professional affiliation and experience conducting RWD analyses in the past 5 years (categorized as 1-5, 6-19, 20-49, 50+ studies), then for responses to the following items using a 7-point Likert scale (from 1 = "very difficult" through 7 = "very easy"):

- Drawing on your experience in conducting these [RWD] analyses over the past 5 years, in those instances in which you were involved in ***identifying fit-for-purpose RWD sources***, please rate how difficult or easy you found it on average. (Hereafter referred to as "Identifying RWD Sources.")
- Drawing on your experience in conducting these analyses over the past 5 years, in those instances in which you were involved in ***assessing the quality & completeness of the RWD sources***, please rate how difficult or easy you found it on average. ("Evaluating RWD Sources.")
- Drawing on your experience in conducting these analyses over the past 5 years, in those instances in which you were involved in ***identifying a rigorous study design***, please rate how difficult or easy you found it on average. ("Identifying Study Design.")
- Drawing on your experience in conducting these analyses over the past 5 years, in those instances in which you

were involved in ***identifying appropriate codes (eg, ICD, CPT, NDC, etc) and developing algorithms to select study patients***, please rate how difficult or easy you found it on average. ("Coding Study Patients.")

- Drawing on your experience in conducting these analyses over the past 5 years, in those instances in which you were involved in ***identifying appropriate codes (eg, ICD, CPT, NDC, etc) and developing algorithms to select interventions of interest and assign patients to treatment groups***, please rate how difficult or easy you found it on average. ("Coding Treatment Groups.")

> Is the task of defining computable operational definitions to select study patients, assemble them into comparison groups, track their comorbidities and concomitant medications, and assess treatment outcomes a less painstaking undertaking, or more?

- Drawing on your experience in conducting these analyses over the past 5 years, in those instances in which you were involved in ***identifying appropriate codes (eg, ICD, CPT, NDC, etc) and developing algorithms to specify patient covariates of interest (eg, comorbidities, concomitant medications)***, please rate how difficult or easy you found it on average. ("Coding Patient Covariates.")

- Drawing on your experience in conducting these analyses over the past 5 years, in those instances in which you were involved in ***identifying appropriate codes (eg, ICD, CPT, NDC, etc) and developing algorithms to specify outcomes of care***, please rate how difficult or easy you found it on average. ("Coding Treatment Outcomes.")

- Drawing on your experience in conducting these analyses over the past 5 years, in those instances in which you were involved in ***selecting the statistical methods***, please rate how difficult or easy you found it on average. ("Selecting Statistical Methods.")

A final item asked respondents to rank order these items directly from most to least difficult.

Figure 1. Distribution of Survey Respondents by Professional Affiliation

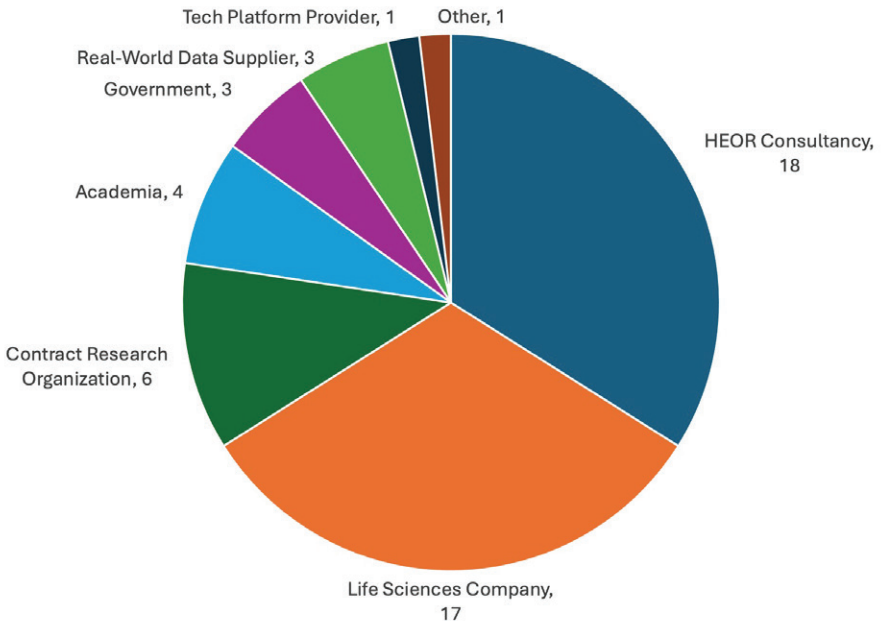
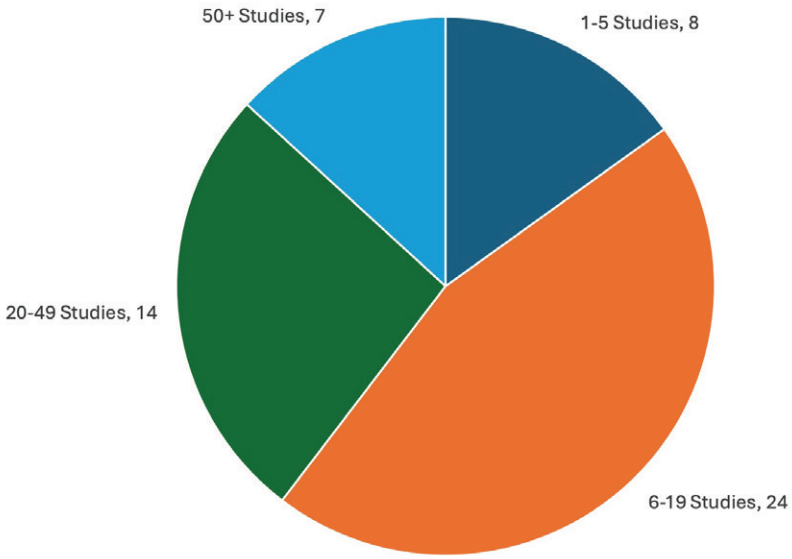


Figure 2. Distribution of Survey Respondents by Real-World Evidence Experience*



**Respondents' real-world evidence experience defined as number of studies performed in past 5 years using real-world data to generate real-world evidence.*

Survey Findings

A total of 53 researchers completed the survey. Most survey respondents worked for HEOR consultancies or life sciences companies (**Figure 1**) and the vast majority had performed at least 6 analyses of RWD in the past 5 years (**Figure 2**).

Respondents directly ranked "Evaluating RWD Sources" as the most difficult task, followed (in descending order) by "Identifying RWD Sources," "Coding Treatment Outcomes," "Coding Treatment Groups," "Coding Study Patients," "Identifying Study Design," "Coding Patient Covariates," and "Selecting Statistical Methods."

These rankings are consistent with the distribution of item responses summarized in the 100% stacked bar chart depicted in **Figure 3**. The color scheme is anchored by cool gray for the neutral response (Likert score of 4) in the center of the 7-point scale, with shades of red for difficult responses (1 to 3), and shades of green for the easy responses (5 to 7). This enables quick visualization of respondents' degrees of difficulty with each of the survey items, with those that are predominantly red being relatively more difficult than those predominantly green. The 100% stacked bar format also allows evaluation of the median (50th percentile) and interquartile range (25th to 75th percentile) of the item responses.

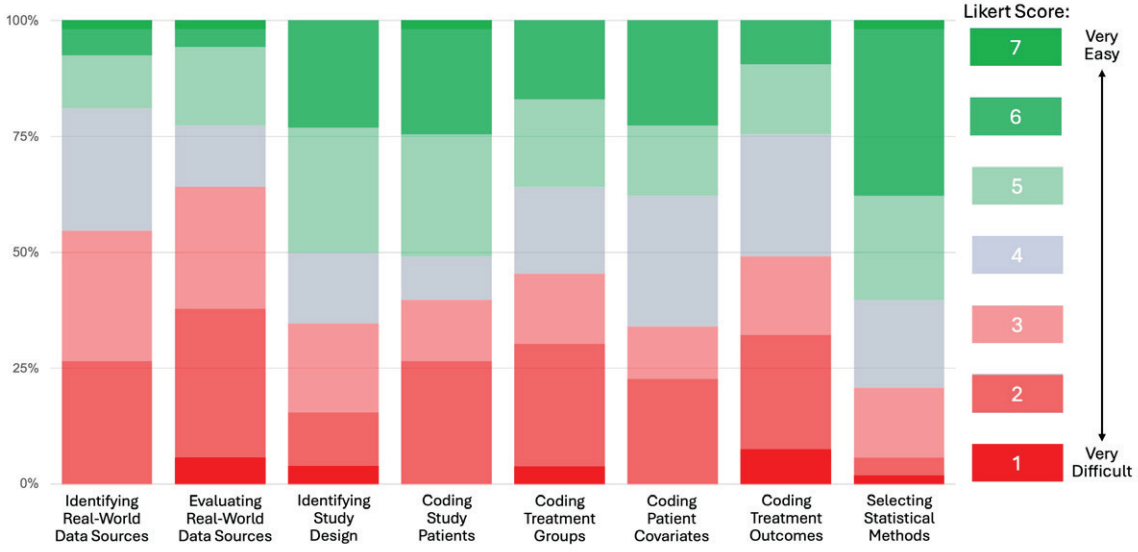
The bar chart shows fairly distinct tiers in terms of researcher difficulties with RWD, with the upfront work of identifying and evaluating RWD sources in the top tier, coding of the data to create analytic files in the next tier, and study design and statistical methods in the lowest tier. It is also interesting to examine how often survey respondents rated items at 4 (ie, as neither difficult nor easy).

What stands out is that relatively few respondents used this rating for "Coding Study Patients," yielding a largely bimodal distribution concentrated in the hard and easy ranges of responses, whereas responses for "Coding Patient Covariates" were more normally distributed, with 4 being the most frequently chosen rating.

> Researchers reported identifying and evaluating secondary data sources to be the most vexing aspects of using RWD to generate RWE.

Subgroup analyses of differences in scale scores by professional affiliation and RWD experience yielded some interesting insights (data not shown graphically). One insight is that experience matters, as there was a clear trend across all items towards higher Likert scores (signifying less difficulty) across the progressive experience categories (ie, 1-5, 6-19, 20-49, and 50+ studies performed in the past 5 years). Differences in Likert scores also were observed by reported professional affiliation. Those working in HEOR consultancies or contract research organizations generally found it more difficult to identify and evaluate RWD sources, and less difficult to construct the analytic files (ie, code study patients, treatment groups, patient covariates, and treatment outcomes) and select the statistical methods. Across most items, the opposite was the case for those working in life sciences companies, as respondents found identifying and evaluating RWD sources somewhat easier and performing the analytics somewhat harder.

Figure 3. Distribution of Item Responses (100% Stacked Bar)



Conclusions & Implications

In this survey, researchers reported identifying and evaluating secondary data sources to be the most vexing aspects of using RWD to generate RWE. Developing code-based algorithms to create the analytic data files (ie, coding study patients, treatment groups, covariates, and outcomes) are somewhat less difficult, with selection of study design and statistical methods relatively straightforward in comparison.

The reported difficulties in assessing RWD sources are interesting considering just how much the RWD/RWE ecosystem has developed in recent years. Guidance documents and checklists for matching RWD sources to research needs/objectives have been issued by ISPOR,[1-2] the US Food & Drug Administration (FDA),[3] and various policy groups (eg, Duke-Margolis RWE Collaborative).[4-5] Some private enterprises have marketed technology platforms to facilitate RWD source identification and evaluation, and even act as brokers for contracting and transfer of data. Whether these efforts have been underutilized, ineffective, or merely need more time to take root is unknown, but the survey results clearly point to RWD identification and evaluation as areas requiring continued attention.

This stands in contrast to issues related to real-world research design and selection of statistical methods for data analysis. Here too, much effort has been made over the past 2 decades to elevate the scientific rigor of research based on RWD, with important contributions from various academic and policy groups as well as both the FDA and European Medicines

Agency. ISPOR also has taken an active role in providing good research practices guidance and educational support programs to researchers interested in generating RWE from secondary RWD sources. Based on the survey findings, it appears that collectively these efforts have indeed made the task of research design and selection of analytic methods relatively easier than other tasks.

The importance of developing "computable phenotypes"—or, more broadly, "computable operational definitions"—has garnered increased attention in recent years. In its guidance document, FDA suggests that "[s]tandardized computable phenotypes enable efficient selection of study populations and ascertainment of outcomes of interest or other study variables for large-scale clinical studies across multiple healthcare systems."[3] To date, however, not enough progress has been made to curate a readily accessible set of standardized and validated computable operational definitions, leading to inefficiencies in conduct of the research. This is confirmed by the survey findings, in which nearly one third of the respondents ranked one of the coding items as the single-most difficult aspect of RWD-based analyses.

In conclusion, this survey highlights the differential progress that has been made in the various aspects of using sources of RWD to generate RWE and points to areas of continued need in the years ahead. Periodic implementation of this survey over time will permit assessment of our continued progress, as this approach to RWE generation increases in importance to health system stakeholders.

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Multistakeholder Healthcare Cooperatives: A New Paradigm for Healthcare Delivery in India

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To achieve universal health coverage by 2030, solutions such as nationalization of the healthcare system or encompassing the whole and diverse country into the folds of insurance are almost impossible.

It is necessary to base the healthcare system on the rules that protect these values and empower people to be self-reliant in health matters ensuring contextual synchronization.

Multistakeholder cooperatives in healthcare delivery can become a reality and pave the way for a novel method of healthcare delivery to achieve universal health coverage and related sustainable development goals.

Background

India is home to a fifth of the world's population. Socioeconomic transition, rapid urbanization, aging population, and climate change make India home to a significant burden of the communicable and noncommunicable diseases.[1] The complex healthcare system in India is resource constrained and is focused on curative aspects, and using technology makes it even more expensive. This drives vulnerable families below the poverty line due to catastrophic out-of-pocket health expenditures.[2] About 70% of people seek healthcare primarily from out-of-pocket expenditure, 10% from insurance, and nearly 20% from the government health system that majorly serves people from lower socioeconomic strata. This percentage is expected to rise to 40% under the coveted Ayushman Bharat Scheme.[3] Heightened expectations and market-oriented healthcare delivery often result in frustration among patients' families, causing occasional incidents of violence against doctors and hospitals.[4]

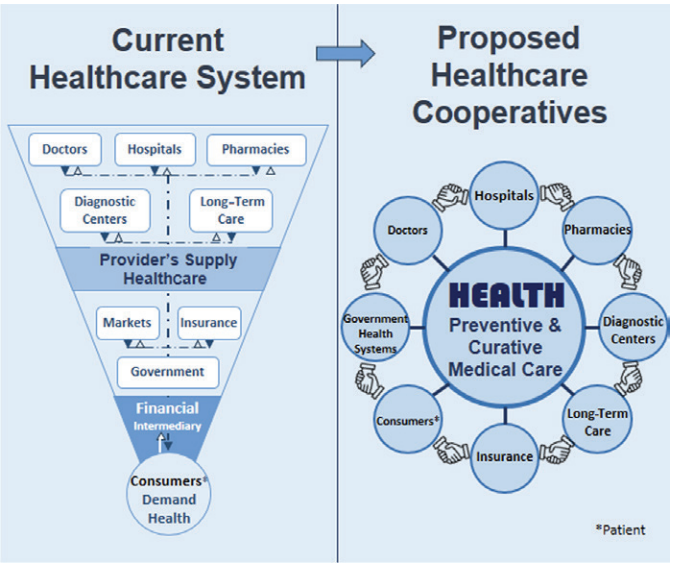
As the problems are at the system level, so must be the solutions. To achieve universal health coverage by 2030, solutions such as nationalization of the healthcare system or encompassing the whole and diverse country into the folds of insurance are almost impossible. Including the private sector in national health programs is not an easy solution either. Can systems engineering give us an answer?

System analysis of healthcare delivery

Healthcare systems are shaped by inherent philosophies and religious backgrounds. But values such as justice, human dignity, and caring for people who need help are common to all. These values, embodied in Hippocratic oath and World Medical Association's declarations, indicate the need for people to be able to care of and make decisions about their health.[5] It is necessary to base the healthcare system on the rules that protect these values and empower people to be self-reliant in health matters ensuring contextual synchronization.

Healthcare systems can be viewed as an organized social response to the health conditions of the population. It is the set of interrelationships between various components of the system that define the characteristics of the system. Components and relationships in the present healthcare system and the proposed one are described in the **Figure**.

Figure. A comparison of current and proposed healthcare systems



Healthcare providers dispense medical care; however, the population desires health and not medical care alone. Government services are highly centralized, nonparticipatory, and resource-constrained. Insurance providers and markets are profit-oriented.

Unfortunately, prevention is better than cure, but preventive services have no markets. In addition, the inputs and outputs of preventive healthcare services are not clearly visible to the stakeholders. The multiple stakeholders in the system with different goals should prioritize population health, and the system should be participatory to preserve the values of human dignity and self-reliance. How can we optimize the system to achieve this?

Proposed multistakeholder healthcare cooperatives

Optimization of the whole healthcare system requires a clear understanding of the goal of the overall system as well as of interactions between the subsystems.

From the financial engineering perspective, the cooperative organization may be a solution to optimize outcomes in this set of diverse portfolios with distributed decision making. Agency theory predicts that agents can behave in bounded rationality and respond altruistically in an appropriate environment.[6]

> Healthcare providers dispense medical care; however, the population desires health and not medical care alone.

Social economy researchers largely predict that such organizations will fail due to the high costs associated with distributed decision making. However, numerous successful examples of multistakeholder cooperatives from Italy and Canada refute this hypothesis.[7] The framework that explains the decision-making in these organizations is the one described by Ostrom about collective management of common pool resources.[8]

Freeman's stakeholder management model, motivated by a sociogram, asserts that multiple stakeholders can come together to achieve common mutually agreeable goals.[9] In this regard, information technology has the potential to link diverse groups on a common platform, allowing each player to get meaningful information about inputs and outputs facilitating effective interaction.

Multistakeholder cooperatives in healthcare delivery can become a reality and pave the way for a novel method of healthcare delivery to achieve universal health coverage and related sustainable development goals. These cooperatives can reconcile the supply and demand of healthcare services by bringing together different stakeholders to jointly manage costs and risks, and to ensure the highest quality of patient-centric care.[10]

Examples of healthcare cooperatives across the world

The International Health Cooperative Alliance estimates that there are more than 100 million households worldwide that are served by health cooperatives.[11] Examples of health cooperatives in developing countries are in Brazil and Argentina. A significant portion of the healthcare market in Brazil is dominated by cooperatives, with Unimed being both the biggest medical cooperative system in the world and the largest medical care network in the nation.[10] In Argentina, cooperatives primarily provide nursing, pharmaceutical, and primary healthcare services. This is because approximately 50% of the population lacks healthcare access due to adverse socioeconomic conditions in the country.[10]

The history of health cooperatives in India dates back to the 19th century. States like Kerala, Karnataka, and Gujarat have been major players in this domain. The positive impact of healthcare cooperatives can be utilized to reduce the burden on health providers, improve accessibility in remote areas, impart health education and awareness, and provide long-term and home care for terminally ill patients.[12]

Developed countries also utilize healthcare cooperatives for providing improved healthcare to the population. For example, HealthPartners, United Ag, Mountain Health Co-Op, Group Health in Washington, and Health Partners in Minnesota are large healthcare cooperatives that have flourished in the United States for the past 50 years. They focus on members' health and well-being and share the profits by providing the best low-cost plans for the members.[13] In Spain and Belgium, pharmacy cooperatives have significant market share to provide people with quality and affordable medicines.[14]

Advantages and disadvantages

Healthcare cooperatives across the world are traditionally where people of similar interests would sell or buy. A major disadvantage of such cooperatives is that one member has one vote for a governing board member by which the system can become a prey to political and other pressures. Multistakeholder cooperatives are a different concept that bring multiple stakeholders in the field of healthcare together in a network of shared investment and profits. The government needs to facilitate the emergence of such cooperatives by advising a regulatory, economical, and legal framework.

> What is needed is meaningful cooperation of various stakeholders under a systematic framework to achieve a common goal of "Health for All."

The advantages of proposed multistakeholder healthcare cooperatives in India over traditional systems are that they can provide service range expansion (health promotion and prevention to rehabilitation), social care, pharmaceutical range expansion, cost and risk management, quality improvement, adaptability, and sustainability to cover comprehensive preventive care. Staffing, equipping, and managing a healthcare practice is costly. Healthcare cooperatives support that by increasing the average per member recovery versus individuals who pay out of pocket. Improved profitability can also help enhance care quality, leading to better clinical outcomes. Members can proactively take control of their health by establishing good habits.[10,13]

Conclusion

The application of systems engineering to analyze the healthcare system in India brings forth the solution of multistakeholder cooperatives.

The government of India has already kicked off an initiative, the Ayushman Bharat Cooperative Scheme, in 2020. Although the framework has not yet been widely used, it can serve as a

starting point. Two initiatives under National Health Mission (ie, the Patient Welfare Committee and the Village Health, Nutrition, and Sanitation Committee) can help engage various stakeholders together. India is already setting up the system of electronic health records and has a rich pool of talent in information technology. What is needed is meaningful cooperation of various stakeholders under a systematic framework to achieve a common goal of "Health for All." The balanced provision of preventive care along with curative treatment would go a long way to achieve universal health coverage targets by 2030.[15]

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Improving Access to Molecular Testing to Enable Personalized Treatment in Oncology

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The introduction of targeted therapy for the treatment of cancer has significantly benefited eligible individuals.

For many individuals with cancer, limited access to molecular testing remains a critical barrier preventing optimal care.

Pharmaceutical companies are undertaking a multifaceted approach to address barriers to comprehensive genomic profiling and access to precision medicine for all patients.

Understanding patients' opinions, expectations, and perceptions about genetic testing in cancer is particularly important to make oncology care patient centered.

Molecular testing as an access barrier

The introduction of targeted therapy for the treatment of cancer has significantly benefited eligible individuals.[1-4] As these therapies target key driver alterations to increase tumor response and minimize toxicity, the benefit-risk ratio is optimized for individuals expressing the associated actionable alteration but not for those who do not. Consequently, the use of targeted therapy first necessitates molecular testing, such as genomic profiling, to identify those who will benefit from treatment. Although approved targeted therapies span multiple tumor types and numerous guidelines recommend molecular testing for key alterations to improve patient outcomes, testing rates continue to vary across clinical practice and regions.[5,6] Thus, for many individuals with cancer, limited access to molecular testing remains a critical barrier preventing optimal care. Given the widespread recognition of this issue, there are various efforts to address barriers to access, spanning from industry to the patient level. As the practice of molecular status assessment continues to expand with the discovery of additional actionable alterations and methods continue to evolve in technical complexity,[7] we must not only consider current but also future access barriers.

The industry perspective

Pharmaceutical companies are undertaking a multifaceted approach to address barriers to comprehensive genomic profiling and access to precision medicine for all patients. One key effort focuses on the implementation of quality improvement studies to assess appropriate molecular testing practices at specific hospitals or institutions. These studies include the identification of a specific barrier to testing at the site, a proposed approach to overcome that barrier, and development of a study plan to measure the impact of the change. Current efforts have led to recommendations such as the introduction of nurse navigators and molecular tumor boards to enhance testing and interpretation of molecular reports, the use of innovative in-house sequencing technologies to reduce processing times, the incorporation of reflexive test ordering within the electronic medical record system, and the elimination of cost barriers at locations with in-house testing in traditionally underserved patient populations.

> Although approved targeted therapies span multiple tumor types and numerous guidelines recommend molecular testing for key alterations to improve patient outcomes, testing rates continue to vary across clinical practice and regions.

As these studies progress, publication of these data and use of this evidence will support advocacy for practice pattern changes, including increased adoption and utilization of high-quality comprehensive biomarker testing for patients who need it most.

The patient experience

While molecular testing efforts are focused on enabling use of a targeted therapy, data from genetic testing to determine prognosis of individuals with cancer have helped highlight challenges with testing at the patient level. For example, there are concerns that undergoing a genetic test and receiving an uncertain result could have a psychological impact on individuals with cancer.[8] Understanding patients' opinions, expectations, and perceptions about genetic testing in cancer is particularly important to make oncology care patient centered.

Although precision medicine has been life-changing for millions of patients, particularly in the breast cancer space, there are numerous barriers to its equitable implementation. Specifically, there is evidence of racial and geographic

disparities in molecular testing in cancer in the United States, as well as disparities between Indigenous and non-Indigenous populations in accessing clinical genetic care in Australia.[9,10] When eliciting patient perspectives and addressing barriers to genetic testing in oncology, it is important to avoid exacerbating existing disparities.

> There are numerous barriers to access to molecular testing to enable precision medicine, and addressing these barriers will require collaboration across many stakeholders, including HEOR groups and pharmaceutical companies.

An example of current work to better understand geographic disparities in molecular testing is the *Precision Care for Men With Prostate Cancer in Tasmania—PC4PC-TAS Study*. The ongoing study is led by investigators at the Menzies Institute for Medical Research, University of Tasmania, and national and international collaborators. A major component of this study, which focuses on individuals with prostate cancer living in a regional area, is gaining insight into the experience and perceptions of patients regarding genetic testing. In the recently completed first phase, researchers spoke with participants to understand their knowledge of "precision medicine" and gain insight into their concerns and expected support needs when undergoing genetic testing for their cancer. In the second phase, the team will work with participants, their caregivers, and clinicians to identify important patient-centered outcomes. Outcomes in this study will be published and presented at future scientific meetings to further the evidence base in this area.

Summary

Precision medicine is an exciting development in oncology that has been life-changing for millions of individuals with cancer. There are numerous barriers to access to molecular testing to enable precision medicine, and addressing these barriers will require collaboration across many stakeholders, including HEOR groups and pharmaceutical companies. In addition, collaborations within stakeholder groups through consortiums and advocacy groups will help develop more informed studies to address these barriers to testing. It will also be essential to engage patients in these studies to ensure that the questions being asked are meaningful to individuals with cancer and address their needs. By working together, we will address barriers to molecular testing and get the right therapy to the right patients at the right time.

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Application of Real-World Data Sources for Equity-Informative Evaluations in the United States: A Multiple Myeloma Case Study

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In the United States, significant disparities in multiple myeloma disease incidence, access to care, and outcomes exist among sociodemographic groups.

Leveraging real-world data is essential for assessing the extent of health inequities and their impact on multiple myeloma treatment outcomes.

Coordinated efforts from the general public, advocacy groups, healthcare providers, policy makers, and pharmaceutical companies will be required to address disparities in individuals diagnosed with multiple myeloma. Integrating health equity into health technology assessment and utilizing real-world data can drive improvements in multiple myeloma care and promote equity in healthcare delivery and outcomes.

Introduction

Incorporating health equity into value and health technology assessment (V/HTA) is a major focus in health economics and outcomes research, as evidenced by a previous *Value & Outcomes Spotlight* theme (May/June 2024), *Value in Health* papers, and an active ISPOR Health Equity Special Interest Group.[1] Publications from the European Society of Medicine and the Center for Innovation & Value Research emphasize the importance of integrating health equity into healthcare evaluations.[2,3] A common theme is the need for data generation to inform high-quality evaluations on equity-relevant topics. In this article, we examine this topic from a US perspective using multiple myeloma (MM) as a case study and expand on research presented at ISPOR Europe 2023.[4]

MM is a hematologic malignancy characterized by abnormal proliferation of monoclonal plasma cells in the bone marrow. It predominantly affects older adults, with a median age at diagnosis of 69 years. In 2024, 35,780 new cases were diagnosed in the United States, with a 5-year relative survival rate of about 61%.[5] Although novel therapies have greatly improved outcomes, MM remains incurable, and patients often experience multiple relapses and die from their disease.[6]

Health disparities in MM

Disparities in MM outcomes result from a complex interplay of factors. Evidence suggests differences in disease biology between racial and ethnic groups, such as variations in cytogenetics and molecular alterations that could affect prognosis, treatment decisions, and outcomes. The incidence of MM is at least twice as high in Black individuals compared to White individuals, and lowest among Asians and Pacific Islanders.[6]

Despite a higher disease incidence, Black individuals are underrepresented in clinical trials, comprising about 6% of US participants but approximately 20% of US cases.[7] Real-world studies show disparities extend beyond the clinical trials setting, with discrepancies in access to triplet induction treatment, autologous stem cell transplantation (ASCT), and CAR-T cell therapy for these groups. For instance, one study found Black and Hispanic individuals experienced longer times from MM diagnosis to novel therapy initiation compared to White individuals, with median times of 5.2 and 4.6 months versus 2.7 months, respectively.[8] Sociodemographic disparities further exacerbate inequities, affecting access to diagnostic testing, timely treatment, and novel therapies. Socioeconomic factors such as lower income and lack of insurance coverage can negatively influence the likelihood of receiving timely MM diagnosis and treatment, consequently worsening outcomes. For example, a study found that low socioeconomic status was associated with poorer overall survival, showing a 54% increase in mortality compared to those with higher socioeconomic status.[9]

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Disparities in treatment and survival among individuals diagnosed with MM are driven by systemic factors and social determinants of health, along with genetic differences, cultural beliefs, medical mistrust, and variations in disease management. Overcoming these disparities requires a multifaceted approach that considers both systemic and individual factors to promote equity among individuals diagnosed with MM.

Leveraging real-world data

Real-world data (RWD) offer a valuable resource for understanding how MM affects various populations and supporting equity-informative evaluations of MM therapies. By leveraging RWD, researchers can better assess the extent of health inequities and their impact on disease progression and treatment outcomes.

We conceptualized how health inequality-relevant variables influence disease manifestation, access, and outcomes of patients with MM. [**Figure 1**] Race and ethnicity are key factors, as they differentially affect the need for care due to differences in incidence and disease biology, which can impact treatment decisions and access. Sociodemographic factors play a significant role as well. Marital status may indicate the presence of a caregiver and may be associated with the likelihood of receiving an ASCT, leading to differences in outcomes. Socioeconomic factors such as income are essential in determining access to timely diagnosis and treatment options, influencing survival rates and quality of care. When sociodemographic and socioeconomic data are not readily available, residential data can provide valuable contextual information. Area-level variables such as county-level median income can offer important insights into the role of the individual's socioeconomic environment when these variables are linked to RWD that include the patient's ZIP code or county of residence. In fact, our prior work found significant associations between county-level indicators of deprivation and both MM treatment type and subsequent outcomes.[10]

Multiple data sources fill the gaps

A key question is whether RWD can fill in the evidence gaps that remain owing to underrepresentation of racial and ethnic groups in MM clinical trials.

We reviewed the literature to identify datasets that have been cited in past RWD studies of MM outcomes. Datasets were organized into categories based on key characteristics. We identified and reported patient characteristics that can be employed in MM equity-informative studies. We focused on whether race was reported in these studies, and if so, the proportion of Black patients.

Our findings illustrate the variability in RWD sources. [**Table 1**] Real-world databases like Optum's Clinformatics® Data Mart and the Surveillance,

Figure 1. Health inequality continuum in multiple myeloma and health inequality-relevant variables in real-world data

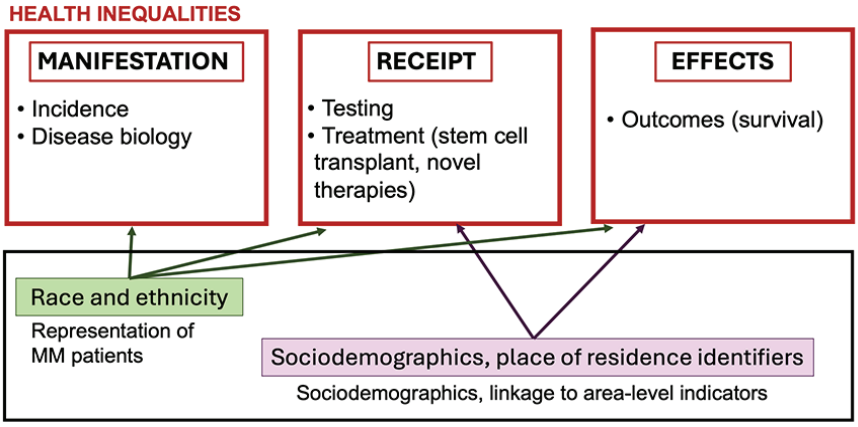

Table 1. Real-world datasets and patient-level characteristics reported in selected MM studies

Data type			Data source example	Data source	Race^,*	% Black^	Place of residence level*	Marital status*	Other*
REGISTRY			National registry	Connect® MM, National Cancer Database	Yes	12.7-21.4	Census tract	No	SES indicators linked from place of residence
	CLAIMS		Linked registry/ Claims	SEER-Medicare	Yes	15-20.9	County	Yes	SES indicators linked from place of residence
			Commercial insurance claims	Optum® Clinformatics® Datamart IQVIA PharMetrics®	Sometimes	14.7-28.2	Census region	No	/
		EMR	Technology platform	Flatiron Health	Yes	20.2	Census region	No	/
			Single institution	Academic medical centers	Yes	18.9-42.3	Exact address, census tract, ZIP code	Sometimes	SES indicators linked from place of residence

EMR indicates electronic medical record; MM, multiple myeloma; SEER, Surveillance, Epidemiology, and End Results; SES, socioeconomic status.
^Reported frequencies for Black patients included in the cohort.
**Information could be available in the dataset, but not utilized or reported for the identified studies.*

Epidemiology, and End Results (SEER) data linked to Medicare claims, cover large populations, making them valuable for understanding healthcare utilization patterns and economic aspects of care. However, these data sources often lack detailed clinical and demographic information, such as race and ethnicity or place of residence. When available, Black patient representation ranged from 14.7% to 28.2%, demonstrating a considerable degree of diversity. Survival outcomes may also be limited in claims data, restricting their use in longitudinal studies.

> By leveraging RWD, researchers can better assess the extent of health inequities and their impact on disease progression and treatment outcomes.

Electronic health records data offer rich clinical details, including laboratory results, treatment responses, and patient histories. They often include sociodemographic information such as race, marital status, and place of residence, allowing for more nuanced analyses of health disparities. However, they are confined to encounters within specific healthcare systems, which may not capture all the care an individual receives. This confinement can also limit their sample size and generalizability. Nevertheless, the clinical and sociodemographic information provided is extremely rich. These data sources can exhibit high representation of Black patients, with single institution data showing such proportions up to 42.3%, the highest among the data sources examined.

Integrating multiple data sources can significantly enrich research findings by combining the strengths of each data type while mitigating their limitations. However, merging data from different sources requires careful consideration of data compatibility and privacy concerns, as well as addressing technological hurdles. Ensuring accurate linkage and maintaining patient confidentiality are critical.

Path to equity: engaging stakeholders

Understanding and addressing disparities requires a coordinated effort from all stakeholders—patients, healthcare providers, policy makers, and pharmaceutical companies—to achieve equity and ensure that all patients receive effective and timely interventions. For healthcare providers, recognizing the disparities in MM is essential for delivering equitable care. Providers can better address diverse patient needs by fostering trust, open communication, and cultural sensitivity and engaging with MM patient communities. Additionally, growing evidence about the impact of disparities in access and outcomes can inform and inspire action. Highlighting successful outcomes of patients with MM across communities who receive high-quality care can encourage best practices and drive improvements in care delivery. The patient's experience with MM care could be influenced by the treatment setting—whether a community practice or academic center—and the characteristics of the treating physician (eg, years of experience, clinical practice setting). Differences in treatment decisions, access to advanced therapies, adherence to guidelines, and facility type can lead to varying patient outcomes. RWD, particularly individual patient data linked to healthcare-, provider-, and hospital-level characteristics, provide an opportunity to study provider-level variations, identify patterns that contribute to disparities, and better understand the relationship between patient demographics, provider behaviors, and care settings.

Policy makers can leverage findings from RWD studies to inform policies that address healthcare inequities, such as promoting diversity in clinical trials and equitable resource distribution. However, using RWD for health technology assessment (HTA) is challenging due to the limited data availability at the time new treatments are assessed. Proactive approaches, including preplanned data collection and the use of modeling techniques, can support equity impact analysis before substantial RWD are available. Combining quantitative RWD with qualitative insights from patient communities can help embed health equity considerations into HTA processes. This aligns with recent calls for standardized health equity frameworks and metrics, allowing assessments to evolve as more data become available.[1-3]

> For pharmaceutical companies, a priority is to understand outcomes across groups who experience access barriers, such as the uninsured or those needing help navigating the healthcare system.

For pharmaceutical companies, a priority is to understand outcomes across groups who experience access barriers, such as the uninsured or those needing help navigating the healthcare system. Mixed methods can be used to understand unmeasured factors and guide improvements to ensure all patient populations benefit from new treatments. These insights can also inform initiatives aimed at increasing representation in clinical trials, such as targeted recruitment efforts and partnerships with community organizations.

Conclusion

The necessity of robust data generation to support high-quality evaluations is a recurring theme across efforts to incorporate health equity considerations into value and health technology assessment. Using MM as a case study in the United States, we illustrate how RWD can serve as an important resource to support equity-informative evaluations and to fill in evidence gaps from clinical trials. Through data-driven approaches, the healthcare community can strive towards increasing equity in value assessments and access to treatment.

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Generative Artificial Intelligence and the Future of Health Economic Modeling

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A 2024 study showed that large language models could be leveraged to rapidly and accurately program complex health economic models in R, without human intervention.

Automatically programming health economic models would enable accelerated model development and could reduce human error. In this scenario, health economists would focus on model design and quality control.

Investment is needed to support further testing and development to realize the potential of LLMs in health economic modeling (including promising indications for Excel-based modeling and model reporting).

Introduction

Generative artificial intelligence (AI) is a field within AI aimed at generating new content (text, image, video, and audio). The field has progressed rapidly in recent years with the development of large language models (LLMs)—large-scale, pretrained, statistical language models based on neural networks.[1]

In the past 12 months, generative AI has emerged as a hot topic in the health economics and outcomes research (HEOR) community. There is a recognition that LLMs offer unprecedented opportunities for enhancing the efficiency, speed, and quality of our work.

> In the past 12 months, generative AI has emerged as a hot topic in the health economics and outcomes research community.

So, what's the fuss about? Firstly, the application of LLMs in HEOR encompasses a wide range of problems that were not previously amenable to AI. Traditionally, AI was limited to classification and prediction.[2] However, LLMs can generate text, code, image, audio, and even video content. While classification and prediction were useful in certain domains of HEOR, these new capabilities are applicable across all domains.

Secondly, LLMs have comparatively low barriers to use. Traditional AI models were developed and optimized for highly specific tasks. LLMs such as OpenAI's GPT-4o have demonstrated an extensive degree of versatility, performing tasks as varied as debugging code, translating text, and interpreting images. Given the above, it's no wonder there is a rush to explore applications for LLMs across HEOR.

LLMs are expected to have a large impact in health economic modeling. The process of building, adapting, reporting, and quality controlling health economic models is often repetitive, time-consuming, and prone to human error. Through application of LLM-based methods, there are opportunities to enhance the efficiency, speed, and accuracy of our modeling. This article aims to shed light on the future of LLMs in health economic modeling. It focuses on the findings of a 2024 study that evaluated the capabilities of GPT-4 in constructing health economic models and concludes with a discussion of what we can expect in the years to come.

A note on using LLMs

Before getting started, it's important to touch on the different ways in which LLMs can be used. Most health economists will have interacted with LLMs through a web interface such as ChatGPT. This can be extremely useful for Q&A support; however, more advanced approaches are required to solve complex problems such as those involved in health economic modeling. Just as humans struggle to answer complex questions straight away, an LLM's performance is generally optimized when problems are broken into steps, which can be focused on one at a time.

> LLMs are expected to have a large impact in health economic modeling. Through application of LLM-based methods, there are opportunities to enhance the efficiency, speed, and accuracy of our modeling.

Application programming interface calls (API calls) can be used to build automated LLM toolchains that enable structured approaches to problem solving. Figures 1 and 2 demonstrate 2 different approaches to asking an LLM a question.

Figure 1 visualizes a simple approach, mirroring interactions with ChatGPT. Figure 2 visualizes an automated toolchain, which enables structured problem solving. The colored LLMs in Figure 2 represent that models primed with different instructions and context can be used at different points in the chain, optimizing their performance on a specific subtask. For those who are interested in applied LLM methods, a good place to start is: https://platform.openai.com/docs/guides/prompt-engineering/six-strategies-for-getting-better-results.

Are LLMs good modelers?

In March 2023, GPT-4 was released. This was widely regarded as a step change in the capabilities of LLMs. GPT-4 demonstrated impressive abilities in writing code, and this inspired my colleagues and me, as well as our collaborators at Bristol Myers Squibb, to investigate the capabilities of GPT-4 in health economic modeling. After several months of testing and refinement, we presented our research at ISPOR Europe, and subsequently published in *Pharmacoeconomics Open*.[3]

> Rather than test GPT-4 directly, we developed an automated toolchain for partitioned survival modeling in R.

The aim of our research was to assess whether GPT-4 could program 2 published health economic analyses in R based on text instructions describing the assumptions, methods, and parameter values that should be used. We focused on R rather than Microsoft Excel because it's an innately more LLM-friendly format (more on this later). The health economic models were partitioned survival models in non–small-cell lung cancer and renal cell carcinoma that were originally developed in Microsoft Excel.[4,5] As any modeler knows, programming a cost-effectiveness model is a complex problem. Therefore, rather than test GPT-4 directly, we developed an automated toolchain for partitioned survival modeling in R (**see Figure 2**). Our chain of LLM interactions used separate instances of GPT-4 primed with contextual knowledge and instructions relevant to specific aspects of health economic modeling. For example, coding the drug acquisition cost calculations or writing code to construct a trace.

To test the performance of the toolchain, we manually developed a set of text instructions (or "prompts") describing the assumptions, methods, and parameters of each cost-effectiveness model (**see Figure 3**). The prompts were supplied and complete R scripts for each cost-effectiveness model were automatically generated without human intervention. As the output of an LLM can vary, we generated 15 scripts for each health economic model to test variability.

Figure 1. Simple interactions with an LLM (eg, ChatGPT)

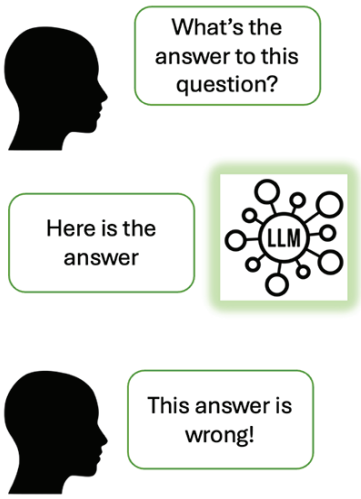
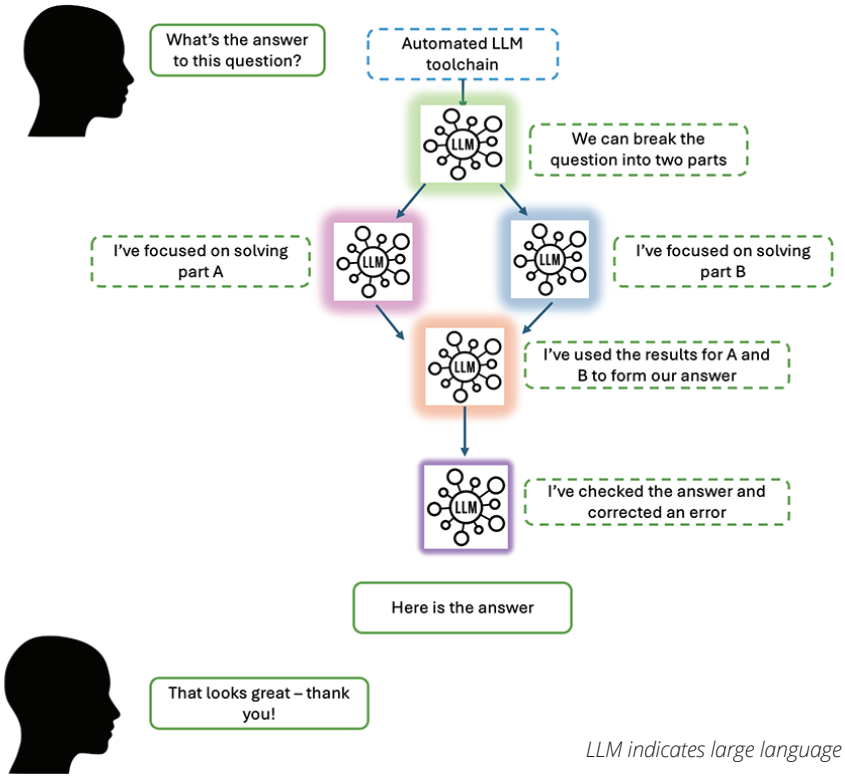


Figure 2. Automated toolchains enable structured problem-solving with LLMs



LLM indicates large language model.

Figure 3. Example prompt

> **The dosing schedule for pazopanib is 800 mg every day. The dosing schedule for sunitinib is 50 mg every day, using a 4-weeks-on, 2-weeks-off repetition. Apply the relative dose intensity for sunitinib and pazopanib after week 29. Assume vial sharing.**
>
> **Pazopanib cost of 60 pills (400 mg) = CHF 4025.75**
> **Sunitinib cost of 28 pills (50 mg) = CHF 5476.25**
> **Relative dose intensity for sunitinib and pazopanib = 1**

The findings of our study were very promising. The AI-generated cost-effectiveness models were created rapidly (average 834 seconds) and accurately (over 73% of scripts were completely error free, and error-free scripts replicated the published incremental cost-effectiveness ratios to within 1%).

> Given the right prompts, complex health economic models can be accurately programmed by LLMs in rapid timeframes.

Hallucinations are an often-cited issue with LLMs. However, we found that creating a sufficiently structured toolchain, providing detailed prompts to describe the cost-effectiveness model design, and priming LLMs with contextual knowledge at each point in the chain, essentially eliminated this problem. Where errors were identified, the vast majority were minor and similar to errors that might be made by a human modeler. For example, omitting a conversion of time units.

What does this mean for health economic modeling?

The research described above demonstrates that given the right prompts, complex health economic models can be accurately programmed by LLMs in rapid timeframes. I believe this has significant implications for how we will build health economic models.

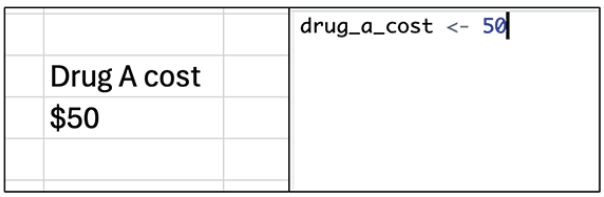
If LLM-based health economic modeling toolchains can be perfected, health economists could automatically program models (such as cost-effectiveness models or budget impact models) following conceptualization. Given that the capabilities of LLMs are continuing to improve, I think this is a strong possibility. Automation would enable rapid and efficient health economic model development and could reduce human error (a 2020 study found that virtually all human-built health economic models contain technical errors).[6] In this scenario, health economists would write model specifications designed for LLMs and quality control AI-generated models. This level of efficiency could support routine exploration of alternative model structures, which are currently rarely performed due to associated costs. Further, short of full adoption, AI-generated health economic models could be used to efficiently perform double programming validation for human-built models.

Health economists can prepare for this future by getting hands-on with LLMs and learning their strengths and limitations. For example, experimenting with ChatGPT to write Excel formulae or provide comments on model code. Note that confidential information should not be submitted to public LLMs and any outputs should be checked by a human.

Regarding the acceptability of AI-programmed models, it should be noted that an AI-generated model is just as scrutable as a human-built model. All calculations, input values, and any other programming are visible and can be quality-controlled in the same manner.

Despite the promising indications, it's important not to overstate what has been achieved so far. There is still much work to do. Chiefly, further studies are required to test the generalizability of LLM-based modeling toolchains across a greater number of disease areas, models, and model types. Developing and improving LLM-based toolchains is time-consuming and requires expertise. To realize the full potential of LLMs in health economic modeling, investment will be required.

Figure 4. R modeling versus Excel modeling



Looking forward

So far, this article has focused on an important but narrow application of LLMs to health economic modeling. I'll conclude by touching on some promising indications for applications in other areas.

Excel modeling

As mentioned above, R models are innately more "LLM-friendly" than Excel models. This is primarily because Excel models require a greater level of interpretation. Consider **Figure 4**. In the R model (right-hand side) there is no ambiguity as to what "50" represents; it is the value of the "drug_A_cost" variable. In the Excel model (left-hand side) we need to infer that "50" represents the cost of drug A through the spatial relationship between 2 cells. Despite this challenge, some promising early research has demonstrated the feasibility of using LLMs to adapt Excel-based cost-effectiveness models, see: https://tinyurl.com/5n8veatu. Integration of LLMs with Excel-based modeling is likely to rely on consistently structured, "AI-friendly" models.

Reporting

LLMs may also enable automated reporting pipelines for health economic models (see: https://tinyurl.com/4mmj224n). This could be a significant use-case due to the frequency at which model results are extracted (ie, for adaptations, scenario analyses, or when an error is found in the model).

Semiautomation

Finally, most applications I've discussed have focused on end-to-end automation (albeit with subsequent human quality control). A promising area that applications may focus on in the shorter term is semiautomation. This could be particularly relevant where complex processes contain repetitive, simpler tasks. For example, an LLM assistant could be used to construct particular elements of an Excel model (eg, input sheets) in real time during manual cost-effectiveness model construction.

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Q&A

One Man's Vision to Transform Hong Kong Into a Health and Medical Innovation Hub

Interview With Chung-Mau Lo, BBS, JP

Secretary for Health of the Government of Hong Kong

Professor Chung-Mau Lo, BBS, JP, Hong Kong's Secretary for Health, delves into some of the key strategic initiatives for advancing Hong Kong's healthcare and biomedical innovation. Key topics include the integration of the Guangdong–Hong Kong–Macao Greater Bay Area for enhanced clinical trials, addressing the increasing needs of Hong Kong healthcare system, and leveraging international partnerships for global benchmarking.

"The mission is to leverage Hong Kong's high-quality healthcare services and our advancements in research and innovation to position Hong Kong as a leader in the Greater Bay Area and beyond."

– Chung-Mau Lo

PharmaBoardroom: How has your previous experience equipped you for your current role and what are your priorities today as Hong Kong's Secretary for Health?

Chung-Mau Lo: It was with great honor that I assumed the role of Secretary for Health in 2022. This represents the third key area covered in my career at the University of Hong Kong. First, I worked as a liver transplant surgeon, where I worked on surgical innovation for the benefit of patients.

Then, I was deeply involved in healthcare reform in Mainland China, leading the University of Hong Kong-Shenzhen Hospital, an incredible hospital by any global standards. Over the 10 years I spent at that institution, it served as a major platform for piloting healthcare reforms.

Upon embarking on this third phase of my career as Secretary for Health, I set forth 3 key missions. The first was to implement an evidence-based approach to overcoming COVID-19. Within nine months, we transitioned to normalcy from the severe fifth wave in Hong Kong, ultimately lifting the mask mandate.
The second mission is to enhance and continuously improve healthcare services in Hong Kong. While we have an excellent and highly efficient healthcare system, it is crucial to keep pace with rapid advancements in medicine. Utilizing outdated treatments, even from just a decade ago, is not an option.

The third mission is to leverage Hong Kong's high-quality healthcare services and our advancements in research and innovation to position Hong Kong as a leader in the Guangdong–Hong Kong–Macao Greater Bay Area (GBA) and beyond. With nearly 40 years of experience in the medical field, I firmly believe in leading

rather than following advancements. For instance, in liver transplantation, we were the first to develop the right-lobe living donor liver transplant technique, significantly improving patient outcomes.

During my time at the University of Hong Kong-Shenzhen Hospital, we successfully combined Hong Kong's healthcare management with the Chinese healthcare system to find an optimal healthcare management model, which was later adopted by the national government. Back in Hong Kong, my goal is to transform the region into a health and medical innovation hub, as outlined in the Chief Executive Policy Address in 2023. This vision was inspired by my experience at the University of Hong Kong-Shenzhen Hospital and I believe the timing is perfect for this transformation.

PB: How is Hong Kong overcoming the challenges of conducting large-scale clinical trials and securing market registration for medical products, given its relatively small population?
C-ML: Historically, Hong Kong's population of 7.5 million posed significant challenges for large-scale clinical trials beyond phase I. We could only contribute a limited number of candidates for multicenter trials, making it unattractive for pharmaceutical companies to register their products here due to the small market size. However, two pivotal developments have changed this landscape.

Firstly, the GBA initiative has fundamentally redefined our approach. Hong Kong is no longer working in isolation. Pharmaceutical companies conducting clinical trials here now have access to a potential market of 86 million people within the GBA. This integration, driven by national policy and championed by President Xi, has been in progress for 5 years.

Secondly, the GBA initiative addresses the registration system and pricing concerns. We are progressing towards higher integration and standardized practices between Hong Kong and Mainland China. While under "one country, two systems" the drug registration systems differ—with the National Medical Products Administration (NMPA) in the mainland and the Department of Health's Drug Office in Hong Kong—a special measure now allows Hong Kong-registered drugs and medical devices used in public hospitals to be used within designated healthcare institutions operating in the GBA, even if they are not yet registered with the NMPA. This measure, endorsed by the Central People's Government, the NMPA, and other authorities, represents a significant advancement.

> My goal is to transform the region into a health and medical innovation hub.

This initiative is already in effect. I was leading in its implementation. The University of Hong Kong-Shenzhen Hospital was the first pilot site for this measure, demonstrating how drugs registered and used in Hong Kong, but not yet in Mainland China, can be effectively utilized in the hospital setting in GBA. This innovative approach addresses both patient volume and market registration challenges, positioning Hong Kong as a key player in the medical innovation landscape.

PB: How is the payment system managed for Hong Kong-registered drugs and medical devices used in the GBA, considering the different healthcare systems in place?
C-ML: The process involves sourcing drugs from Hong Kong and importing them with a special license through customs for use in hospitals. The drugs are charged at cost under the National Health Insurance of Mainland China, so Chinese patients do not rely on the Hong Kong financing system. This arrangement is part of a special measure to address the lag in the NMPA's registration process. Many advanced drugs and devices used in Hong Kong are not yet registered in Mainland China, which previously led many mainland patients to seek these treatments in Hong Kong.

> While under "one country, two systems" the drug registration systems differ, with the National Medical Products Administration (NMPA) in the mainland and the Department of Health's Drug Office in Hong Kong–a special measure now allows Hong Kong-registered drugs and medical devices used in public hospitals to be used within designated healthcare institutions operating in the Greater Bay Area, even if they are not yet registered with the National Medical Products Administration.

With the development of the GBA, there is a push to improve healthcare services, including access to advanced drugs and devices. The rationale is that if these medical products are safe, effective, and used in Hong Kong they should also be available in selected healthcare institutions in the GBA. This measure ensures that Hong Kong citizens working and living in the GBA receive a similar level of care, and it significantly raises the healthcare standards in the region.

The pilot program began in 2021 at the University of Hong Kong-Shenzhen Hospital and lasted until July 31, 2021. It has since expanded to 19 hospitals, with 32 drugs and 31 devices now available. The process is controlled and cautious, allowing a green channel for these advanced medicines and devices specifically for the GBA. This initiative not only improves healthcare standards but also provides drug companies with a pathway to collect real-world data, which is crucial for formal registration with the NMPA.

We are also planning to develop a GBA International Clinical Trial Institute to further enhance our capabilities in conducting clinical trials and advancing medical innovation. This will facilitate the collection of real-world data from patients, helping in the

formal registration process and ensuring that advanced medical treatments are available to those who need them.

PB: How significant is the recent move in Hong Kong to accept just one international certificate of pharmaceutical product rather than two? Was it a difficult decision to take?
C-ML: The transition from secondary to primary evaluation is the ultimate goal of our regulatory authority, the Center for Medical Products Regulation. The "1+" mechanism is a critical intermediary step in this process. It provides a much faster route for new drug registration by eliminating the delays typically associated with attaining a second certificate of pharmaceutical product.

> Our role is to coordinate and facilitate, not impose.

This streamlined approval process accelerates the registration of innovative drugs and devices from both the Western world and Mainland China, where the biomedical industry is advancing rapidly. The "1+" mechanism allows us to build the necessary expertise and talent pool, preparing us for primary evaluation. Additionally, this period is being used to enhance our clinical trial facilities and capabilities. The GBA offers a significantly larger clinical sample capacity and market potential, which we are leveraging through the development of the GBA International Clinical Trial Institute.

PB: The GBA International Clinical Trial Institute is expected to be operative before the end of 2024 and, although you are clear on its synergetic role, some stakeholders worry this could introduce additional bureaucracy. Why is a centralized body essential for this initiative?
C-ML: When the government initiates a project, skepticism from vested interests is common. However, our role is to coordinate and facilitate, not impose. Currently, clinical trials in Hong Kong are managed in a fragmented manner by institutions like the Clinical Trial Center at the University of Hong Kong and the Chinese University of Hong Kong. While these centers conduct trials, their scale and impact are limited.

Our goal is to coordinate on a much larger scale, leveraging the 86 million population in Mainland China. We are utilizing the Hetao Shenzhen-Hong Kong Science and Technology Innovation Cooperation Zone, which is a national policy directive. The Shenzhen Park work plan, issued by the Central People's Government State Council last August, explicitly aims to develop a GBA international clinical trial center through Shenzhen-Hong Kong cooperation.

This initiative aligns with Hong Kong's role in the 14th 5-Year Plan to become an international innovation and technology hub. Biomedical technology is a significant focus area. Hong Kong is well-positioned for this due to our excellent healthcare services, efficient healthcare system, and robust talent pool. The Hospital Authority's information technology system, which integrates 43 hospitals and 11 million patient records, exemplifies our advanced infrastructure.

Although there have been complaints about data access, we are currently addressing these issues. By integrating and coordinating efforts within the Hetao area and beyond, we aim to create a more impactful and efficient clinical trial environment, benefiting both academia and industry.

Our goal is to facilitate all aspects of clinical trials, including providing resources. Some critical elements require government involvement to function effectively. First, we need to manage the cross-border movement of biosamples and clinical data. Effective coordination with the Shenzhen government and the Central People's Government is essential for the seamless transfer of data and samples across borders, which is crucial for running clinical trials in the GBA.

We will establish central data banks, biobanks, and possibly core laboratory facilities in the Hetao area. These facilities will ensure the security and standardization of data and samples. By having a core facility at the border, we can facilitate the coordination and secure management of these crucial elements.

In addition to coordination, we are integrating public and private hospitals. Currently, university Clinical Trial Centers must seek approvals from multiple research ethics committees/ institutional review boards for cross-cluster clinical research, which can be cumbersome. We are implementing a centralized institutional committee review board for the 43 public hospitals managed by the Hospital Authority in Hong Kong to facilitate single application and single approval of cross-cluster clinical research.

> Addressing the shortage of trained personnel is essential, and our approach involves both local training and international recruitment.

With one protocol, one data bank, and one computer system, researchers can access necessary data to prepare protocols and plan new studies. This integration will allow drug companies to access demographic and patient data, facilitating the planning and execution of clinical trials. This centralized system is already being piloted with the science park, providing a robust framework for future clinical trials.

PB: Given the strain on healthcare resources, how do you plan to address the potential shortage of trained personnel for clinical trials in Hong Kong?
C-ML: Addressing the shortage of trained personnel is essential, and our approach involves both local training and international recruitment. Hong Kong has a strong track record in this regard, supported by our two leading medical schools. The GBA International Clinical Trial Institute will play a crucial role as a training center for clinical trial personnel. We are finalizing discussions with the Shenzhen Municipal Government and the Shenzhen Health Commission to establish the GBA International Clinical Trial Center, as outlined in the Shenzhen Park Work Plan. This collaboration between Hong Kong and Shenzhen is integral to our national strategy.

PB: Considering the differences in medical education between Mainland China and Hong Kong, how do you manage these variations in the context of clinical trials and medical practice?
C-ML: The medical curricula in Mainland China and Hong Kong differ, with programs ranging from 5 to 8 years in China. However, we have accredited 17 of their medical programs for special registration in Hong Kong. Graduates from recognized institutions, such as Shanghai Fudan University and Sun Yat-sen University, can practice in public healthcare institutions in Hong Kong under special registration. After working satisfactorily for 5 years and obtaining a specialist qualification, they will be granted full registration. This approach respects the global diversity in medical education systems.

In clinical trials, we leverage Hong Kong's high standards of quality with the patient volume available in Mainland China. Two key factors make this an opportune time for establishing an innovation hub: the 5-year progress of the GBA initiative and significant improvements in China's healthcare system due to ongoing reforms. Ten years ago, collaboration would have been challenging due to the reliance on drug sales for income in mainland hospitals. Doctors had to sell drugs to supplement their low salaries, which was not conducive to evidence-based healthcare.

> Graduates from recognized institutions can practice in public healthcare institutions in Hong Kong under special registration. This approach respects the global diversity in medical education systems.

However, with the zero-markup policy on medicines implemented about 9 years ago, doctors no longer rely on drug sales for income. This shift has enhanced professionalism and evidence-based practice. Now, doctors prescribe drugs based on their efficacy and necessity for patient health, creating a more conducive environment for clinical trials.

PB: Many years ago, the GBA concept seemed more theoretical than practical. While conducting clinical trials is promising, what is the ultimate goal of this initiative and how do you plan to elevate the entire ecosystem towards biomedical innovation?
C-ML: The GBA initiative offers a tremendous opportunity to transform the biomedical innovation landscape, particularly for rare diseases. Take osteogenesis imperfecta as an example, a genetic disorder causing brittle bones. In Hong Kong, with our low birth rate, only 2 or 3 cases are seen annually, making research and training difficult. Drug companies typically aren't interested in such small numbers.

However, at the University of Hong Kong-Shenzhen Hospital, we established the only center for osteogenesis imperfecta in southern China, seeing 200 to 300 cases each year. We regularly perform surgeries to reinforce these children's bones, providing a wealth of data and clinical experience. This scale is invaluable for research on rare diseases.

Leveraging Hong Kong's resources and the larger patient base in the GBA, we can significantly enhance research and development efforts. Rare diseases are never rare in mainland China as the large population means more cases to study and treat, creating a gold mine for research, education, and training. The advancements in healthcare infrastructure and policy support better diagnosis and treatment, offering a robust environment for clinical trials and biomedical innovation.

In Mainland China, the perception of rare diseases is evolving, and the government's zero-markup policy on medicines has shifted focus towards evidence-based healthcare. This environment is conducive to high-quality clinical trials and the development of new diagnostics and therapies. By integrating Hong Kong's high standards with the patient volume in the GBA, we can create a thriving ecosystem for biomedical innovation, benefiting both researchers and patients.

PB: During your visit to Geneva you discussed regulation and prequalification with the WHO. Can you elaborate on Hong Kong's efforts to achieve ML3 and ML4 status and how this aligns with your broader goals for biomedical innovation?
C-ML: During our visit to Geneva, we met with WHO experts on regulation and prequalification, including Rogério Gaspar, PharmD, PhD, the director. He was very supportive and encouraged us to pursue WHO Global Benchmarking Tool maturity level ("ML")3 status first. Achieving ML3 and eventually ML4 is integral to our strategy to enhance Hong Kong's global standing in biomedical innovation.

Countries like Singapore and Korea have achieved LM4 in recent years, and Saudi Arabia joined them last year. This status is crucial for advancing vaccine manufacturing and other specialized areas. Dr Gaspar emphasized Hong Kong's unique position under the "one country, two systems" framework. While we are part of China, our international orientation makes us an ideal bridge for China to engage with the global benchmarking system.

Our objective is to leverage this unique position to propel our biomedical innovation efforts. Achieving LM4 would be prestigious and highly beneficial for Hong Kong, especially in the realm of vaccine manufacturing. The expansion of the Hong Kong-Shenzhen Innovation and Technology Park will further support these initiatives. We are committed to this goal and will continue to collaborate with international partners to make it a reality.

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