

JANUARY/FEBRUARY 2023 VOL. 9, NO. 1

VALUE & OUTCOMES SPOTLIGHT

A magazine for the global HEOR community.

Addressing Assessment and Access Issues for Rare Diseases



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VALUE & OUTCOMES SPOTLIGHT

JANUARY/FEBRUARY 2023
VOL. 9, NO. 1

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VALUE & OUTCOMES SPOTLIGHT PUBLISHING, SUBSCRIPTION, AND ADVERTISING OFFICE:

Value & Outcomes Spotlight
Online: ISSN 2375-8678
Published bimonthly by:
ISPOR
505 Lawrence Square Blvd, S
Lawrenceville, NJ 08648 USA

Direct photocopy permission and reprint
requests to Director, Publications.

Cover photo courtesy of iStockphoto/dvarg

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FROM THE EDITOR

Being Aware of Rare Disease

As we promote February as Rare Disease Awareness Month and recognize Rare Disease Day on February 28th, it is important for all stakeholders to raise awareness of rare diseases. People living with these diseases (the majority of which are children) and their families deserve our attention and a sense of urgency in improving health and patient outcomes.

In the United States, a rare disease is defined as *a disease or condition that impacts less than 200,000 people*. The European Union defines a rare disease as *a disease affecting less than 1 in 2000 people*. It is estimated that there are about 6000 to 7000 known rare diseases, collectively affecting about 1 in 10 people (or 30 million people) in the United States and 5% of the worldwide population (approximately 300 million people). Among the known rare diseases, approximately 72% are genetic, while those remaining are rare cancers or result from infections (bacterial or viral), allergies, and environmental causes. There are an estimated 200 rare cancers (1 in 5 cancers is rare) and the 5-year survival rate is lower for patients with a rare cancer than for those diagnosed with a more common one.

Unique challenges are associated with rare diseases including diagnoses, treatment, and patient access. Many individuals living with a rare disease have often struggled for years before receiving an accurate diagnosis, with some remaining undiagnosed for a decade or longer. This situation becomes very frustrating and expensive to patients who endure countless physician visits, emergency room and hospital visits, unnecessary tests and procedures, and—in many cases—numerous erroneous diagnoses before the correct diagnosis is made. Once an accurate diagnosis is made, seeking answers and treatment options can be a lengthy process as well, often leaving patients and families frustrated. For improvement to occur, we must listen to patients and their families and fully engage with them as patient advocates.

One landmark in the recognition of rare disease was the passage of the Orphan Drug Act, incentivizing biopharmaceutical companies to invest and develop drugs for these diseases. As a result, hundreds of drugs for rare diseases have been approved by the US Food and Drug Administration, and many more are on the horizon. However, we still have much work to do as approximately 90% of rare diseases still do not have a treatment.

Despite these incentives, rare disease clinical trials and drug development still face numerous challenges. Some of these include lack of understanding of the natural history of the disease, severity of the disease, low disease prevalence, small and heterogeneous patient populations, inadequate understanding of clinically meaningful endpoints, lack of tailored health technology assessment (HTA) methods, no established standard of care, and failure to assess clinical benefit and achieve full approval. Another issue is gaining access to patient data as rare disease patients are often challenging to locate, patient information is inaccessible, and perceived privacy issues and ownership of the data complicate its dissemination and utility. Our feature article focuses on addressing assessment and access issues for rare diseases including the methodologies of HEOR and HTA assessment and the role of patients in value assessment. Additionally, the By the Numbers section provides 7 effective market access strategies to accelerate patient access to orphan drugs.

As healthcare and HEOR professionals seeking to improve health outcomes, we must engage with patients and their families in partnership with patient advocacy groups to leverage their knowledge and experiences in understanding the effects and burdens of these diseases. By listening to their voices, we can work together to motivate all stakeholders, foster collaboration, and accelerate improvements that impact patient outcomes and support their optimal health.

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*



ISPOR SPEAKS

Amplifying the Impact of HEOR Through Continued Advancement of Our Mission

Nancy S. Berg, CEO/Executive Director, ISPOR

It is always a pleasure to look into the future by recapping some of the hundreds of investments your Society has planned for 2023. If you raised an eyebrow at the mention of “hundreds” of investments, know that hundreds is probably an understatement given the activity level of ISPOR members and groups across the globe. Members are the heart of ISPOR—they contribute as strategists, as the Society’s volunteer workforce, and as consumers of programs, content, and engagement that support and inspire the entire HEOR community. And, it is this community that delivers evidence on which decision makers and patients rely.

In early 2023, ISPOR made a significant addition to its member benefits by launching the *HEOR Learning Lab*™ that is now available to all members. *HEOR Learning Lab* provides unlimited on-demand educational video content to facilitate learning and innovative approaches in the field. ISPOR members can immediately access everything that *HEOR Learning Lab* offers, such as video 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 (HTA), economic methods, healthcare financing, access and policy, learning healthcare systems, and much more. More than 500 on-demand content sessions are currently available on the platform!

I am enthused about the ongoing dialogue ISPOR maintains with influencers by encouraging their understanding and utilization of HEOR as important tools for supporting decision making and advancing healthcare.

This year ISPOR will also be launching a communications campaign designed to “amplify” the awareness of HEOR and the work of ISPOR members. This campaign represents a significant investment by the Society and is being designed to increase the awareness and understanding of HEOR to advance its application and use to improve healthcare decisions.



In 2023, ISPOR will also introduce a new conference format that combines valuable in-person experiences as well as a digital option. The new Digital Conference Pass will provide unlimited on-demand post-conference access to conference sessions, as well as a Key Insights session that will summarize the main topics, discussions, and takeaways from the conference. The ISPOR in-person experience is unmatched, and we plan to enhance the conference design to create even greater value for attendees—whether they are participating in the live conference or the Digital Conference Pass and Key Insights event.

In 2023, ISPOR task forces are continuing the development of important Good Practices Reports; special interest groups, chapters, and communities are diligently discussing key topics of interest; the Society’s journals and publications are ever evolving in prominence and scale; and committees and councils are actively advising ISPOR on member interests and needs.

With all that activity underway, I am also enthused about the ongoing dialogue ISPOR maintains with influencers by encouraging their understanding and utilization of HEOR as important tools for supporting decision making and advancing healthcare. Not everyone is aware of the regular decision-maker dialogue taking place within ISPOR, but it is significant and critical at a time when unprecedented policy and decision-making changes are happening—particularly in Europe related to joint clinical assessment and joint procurement, and in the United States with drug price negotiations within the Centers for Medicare & Medicaid Services (CMS). Below are some examples of important dialogue:

- A strategic initiative to engage payers in ISPOR continues to foster greater appreciation for the value and understanding of HEOR in decision making
- Regularly organized discussions with HTA bodies around the world take place through the Health Technology Assessment Roundtable Series held in Europe, North America, Asia, Latin America, and the Middle East and Africa

- ISPOR also routinely sponsors roundtable discussions with patient-engagement groups and is engaging with healthcare providers and other stakeholders
- The Society's policy webinars update members on key issues within their regions and 2 new ISPOR policy sessions will be held this year at ISPOR 2023 in Boston and ISPOR Europe 2023 in Copenhagen

What YOU do as researchers and decision makers is vital to help understand and overcome these challenges, ultimately getting life-saving medicines to patients.

- Engagement and dialogue continues with EUnetHTA, the European Commission, trade groups, and societies with mutual interests, as well as discussions with EMA, FDA, and other regulators and other decision makers worldwide
- ISPOR also routinely responds to formal calls for comments by agencies and organizations through which your Society presents views on strengthening the rigorous use of HEOR science in decisions and change

It is a bit bittersweet that I end this article with communication of my planned retirement at the end of the first quarter, after a 40-year career working for scientific and technical societies. I am leaving a strong organization—financially stable and well-positioned to make even greater impact in the coming years. The search committee responsible for recommending and hiring my replacement has done an outstanding job of selecting from hundreds of applicants. I sincerely thank the members of the Board of Directors that I have worked with for the past 8 years for their vision and support of my extraordinary team and me. The change and progress ISPOR has made is truly remarkable and to sit on a perch that witnesses healthcare from the lens of many stakeholders has been a privilege.

Science and technology have driven considerable advancements in the past several years and their application has changed, challenged, and stretched healthcare systems and decision makers everywhere. What YOU do as researchers and decision makers is vital to help understand and overcome these challenges, ultimately getting life-saving medicines to patients. I thank all of ISPOR for the opportunity to be a part of the organization. My call to you as members is to never lose sight of your incredible role in the big picture: ***the research you conduct or use in decision making impacts us all.***

Best wishes in your future endeavors—I'll be watching for even greater successes (albeit at a distance)!

HEOR NEWS

1 New “Artificial Pancreas” Technology Set to Change the Lives of People Having Difficulty Managing Their Type 1 Diabetes (NICE)

In a draft guidance, an independent NICE committee recommends the use of hybrid closed-loop systems for managing blood glucose levels in type 1 diabetes—technology that has been described as a step towards an artificial pancreas. [Read more](#)

2 Patient Perspectives on Technology-Based Approaches to Social Needs Screening (American Journal of Managed Care)

In trying to understand patient perspectives on completing social needs screening through technology-based modalities such as portals and tablets, researchers found that patients were broadly accepting of screening and recognized the connection between social needs and health. [Read more](#)

3 Chatbots Are Effective in Supporting Self-Management of Depression Symptoms (MobiHealthNews)

A study from the Lee Kong Chian School of Medicine at Nanyang Technological University Singapore examining 9 mental health chatbots found that the chatbots’ coach-like encouragement can help people manage some depression symptoms even though they cannot yet offer personalized advice. [Read more](#)

4 Financing and Funding Gap for 16 Vaccines Across 94 Low- and Middle-Income Countries, 2011-2030

(Health Affairs)

Researchers found a total funding gap of \$38.4 billion between 2011 and 2030 for 16 vaccines among 94 low- and middle-income countries. The decline in development health financing assistance anticipated between 2011 and 2030 outpaces the forecasted increases in domestic government immunization spending. [Read more](#)

5 Scientists Are Finding Increasing Evidence for a Link Between Air Pollution and Neurodegenerative Diseases Like Alzheimer’s (STAT News)

Population studies from around the world increasingly show that there is a connection between air pollution and brain atrophy and cognitive disorders. The superfine particulates in air pollution have been linked to inflammation, cancer, and severe cardiac and respiratory diseases, as well as neurodegenerative diseases. [Read more](#)

6 Statins Could Be a Choice for More People to Reduce Their Risk of Heart Attacks and Strokes, Says NICE (NICE)

While in its updated guidance NICE did not change the cardiovascular disease risk threshold for offering statins, the organization did say the drugs could be an option for people at a lower risk, depending on patient preference or concerns that the patient may be underestimating their risk of cardiovascular disease. [Read more](#)

7 WHO Updates COVID-19 Guidelines on Masks, Treatments, and Patient Care (World Health Organization)

WHO says irrespective of the local epidemiological situation, masks should be worn following a recent exposure to COVID-19, when someone has or suspects they have COVID-19, when someone is at high risk of severe COVID-19, and for anyone in a crowded, enclosed, or poorly ventilated space. [Read more](#)

8 Super-Resistant Mosquitoes in Asia Pose Growing Threat, Study Says (The Japan Times)

An examination of mosquitoes from several countries in Asia and Ghana found a series of mutations had made some of the bugs—particularly those in Cambodia and Vietnam—virtually impervious to popular pyrethroid-based chemicals like permethrin, thus increasing threats from mosquito-borne diseases such as dengue, Zika, and yellow fever. [Read more](#)

9 In China, No Easy Way to Get Pfizer’s COVID Drug Paxlovid (The Japan Times)

Local media reports and online posts bear testimony to the difficulties faced obtaining Paxlovid (nirmatrelvir tablets; ritonavir tablets) in China through official channels, even as Pfizer has shipped millions of doses to that country in the past couple of weeks. [Read more](#)

10 WHO Welcomes Data on COVID-19 in China, Meeting With Minister (World Health Organization)

In its initial analysis of more detailed data about COVID-19 infections provided by Chinese health authorities, WHO notes that the overall epidemiology is similar to waves of infection experienced by other countries, as is the increased pressure on health services. [Read more](#)

FROM THE JOURNALS

A Data-Driven Approach to Support the Understanding and Improvement of Patients' Journeys: A Case Study Using Electronic Health Records of an Emergency Department

Rismanchian F, Hosseinzadeh Kassani S, Mahdi Shavarani S, Lee YH. *Value Health*. 2023;26(1):18-27.

Section Editor: Agnes Benedict

Several terms describe the interactions and transitions of patients in a healthcare system: *patient journey*, *patient flow*, *patient pathway*. Researchers try to capture these concepts and extract the pathways to help policy makers improve healthcare delivery, including making hospitals more efficient by reducing costs and offering quality services to improve patients' experience.¹ Some involve patient interviews and qualitative research; others are based on the immense amount of data that is collected due to the increasing reliance of hospitals on information systems in order to operate on a day-to-day basis.

The understanding of what data analytics methods can deliver has also dramatically increased in the past 10 years. A standard approach to modeling for the purpose of making predictions is to build a theoretical model using current (sometimes qualitative) knowledge of the underlying mechanisms with some degrees of freedom in the parameters, and calibrating the model on specific data in order to make the model ready for prediction. These approaches generally seek a compromise between a

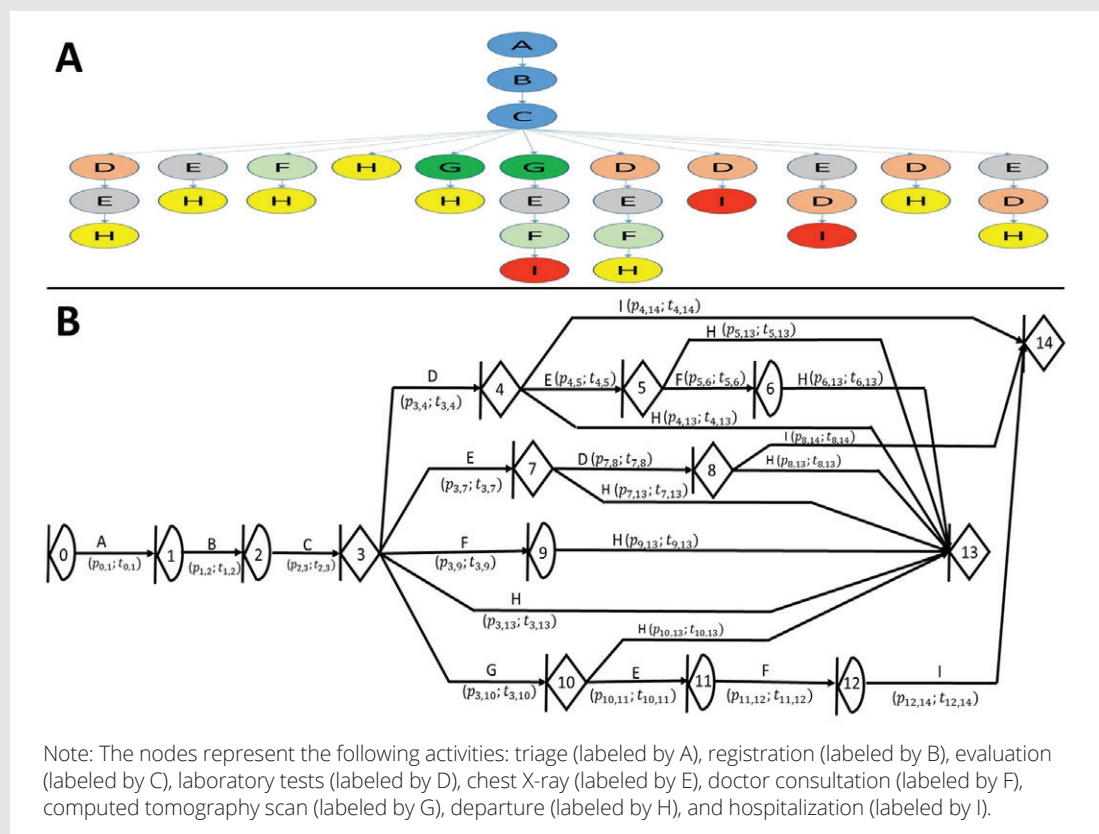
theory of the underlying mechanisms and the observations. However, using the large amounts of data that have become available, there is more widespread use of approaches starting from the data itself, agnostic to the mechanisms (see de Hond 2022² for a description, quality issues, and guidelines in relation to data-driven prediction models applied to healthcare). It is in this context that the authors of this paper propose a methodology to not only depict, but also to model and analyze the patient journey in general, using a data-driven technique called process mining. The authors illustrate the process by creating a model and analysis of performance indicators of data from an emergency department (ED) of a university hospital in Seoul, South Korea.

The data used consisted of patient-level logs of service usage (eg, registration, evaluation by a clinician, laboratory tests, imagery, hospital admission, or departure from the ED). In other words, the authors could follow the pathway of each patient within the ED, in each unit (eg, the laboratory test unit), and at each time stamp. The process-mining technique allowed them to derive a graphical process map. Data were extracted from an information

system whose purpose is primarily administrative. Logs were removed from the analysis if they were incomplete or inconsistent (ie, in terms of timestamps). From the remaining logs, the authors built graphical representations—a process map—of the patients' most typical pathways in the ED, as well as an analytical expression of performance indicators (eg, mean and variance of the full length of stay [LOS] in the ED, the probability of discharge and admission to a hospital ward).

Using graphical evaluation and review (Figure), the authors illustrated how their model and its analysis could generate hypotheses regarding the improvement of the efficiency of the ED. They found that in their case study, LOS was most dependent on the waiting

Figure. (A) Patient journey patterns discovered from the event log. (B) Representation in form of stochastic GERT network.



time in the laboratory tests unit. Therefore, allocating more resources to this unit could support the reduction of mean LOS in the ED overall.

Limitations included that many logs had to be excluded, potentially leading to bias in the results, and there was substantial heterogeneity in the patient pathways that had to be distilled down to a few, and qualitative input from patients and healthcare provided should be used for the interpretation of results.

However, the proposed approach and the detailed documentation of the methods provide an objective and graphical description and analysis of the patients' pathways

in granular yet easily understood dimensions. The author's approach has the potential to identify areas of process improvement and, more generally, areas of focus when seeking efficiency gains and reduced waiting time, ultimately improving the patient experience in a resource-constrained environment.

References:

1. Gualandi R, Masella C, Viglione D, Tartaglini D. Exploring the hospital patient journey: what does the patient experience? *PLOS ONE*. 2019;14(12): e0224899.
2. de Hond AAH, Leeuwenberg AM, Hooft L, et al. Guidelines and quality criteria for artificial intelligence-based prediction models in healthcare: a scoping review. *NPJ Digit Med*. 2022;5(1):2.

RESEARCH ROUNDUP

Section Editor: **Aakash Bipin Gandhi, BPharm, PhD**, Methodologist Expert, RWD, Sanofi, Cambridge, MA, USA

The economic burden of rare diseases: quantifying the sizeable collective burden and offering solutions.

Garrison S, Kennedy A, Manetto N, Pariser AR, Rutter JL, Yang G. *Health Affairs Forefront*. February 1, 2022. doi: 10.1377/forefront.20220128.987667

Summary

The article by Garrison et al summarizes findings from 4 studies across different stakeholders, healthcare systems, and government bodies that highlight the cost burden associated with rare disease conditions. The authors discuss challenges associated with rare disease evaluations and opportunities for future research. The authors also provide recommendations with the aim of addressing gaps and challenges associated with rare disease research.

Relevance

The 4 studies had consensus related to their conclusions regarding economic research of rare diseases. First, the studies acknowledged that rare diseases are responsible for a significant burden on the healthcare systems. At times, this burden is even more significant than that imposed by more prevalent disease conditions. Second, a lack of data that are standardized for rare disease research prevents investigators from identifying and quantifying patients with rare diseases. Third, future analysis requires novel data and approaches to accurately quantify the true burden of rare disease. The authors also summarized the top factors that drive the cost burden of rare disease. These include delayed diagnosis and imperfect quantification of the disease (lack of diagnostic codes), direct medical costs (eg, inpatient admissions), indirect and nonmedical costs (eg, lost earnings due to reduced productivity), and cost of rare disease therapies. Finally, the authors propose certain recommendations to help improve rare disease research. These include creating diagnostic codes for rare disease, enriching the data collection process for rare diseases (eg, through improved electronic health record capture, supporting registries, and natural studies), and improving patient access to advanced diagnostic tools.

How to value orphan drugs? a review of European value assessment frameworks.

Blonda A, Denier Y, Huys I, Simoens S. *Front Pharmacol*. 2021;12:631527. doi: 10.3389/fphar.2021.631527.

Summary

This narrative review by Blonda et al provides information on the strengths and limitations of value assessment frameworks for orphan drugs in Europe that can serve as guide for healthcare decision makers.

Relevance

Standard economic evaluations within value assessment frameworks consider both orphan and non-orphan drugs equally. Hence, the cost-effectiveness estimates of these evaluations do not consider the effect of disease rarity on data uncertainty parameters. This in turn can affect the evaluation of an orphan drug's health benefit as measured in quality-adjusted life-years (QALYs). Hence, value assessment frameworks that allow for the inclusion of weighted QALYs or those that allow for the inclusion of flexible incremental cost-effectiveness thresholds are desirable to overcome disease rarity-related limitations. Multicriteria decision analysis is an approach that allows investigators to include a set of flexible parameters that are inclusive of multiple stakeholder perspectives. In conclusion, all decision makers should aim to seek the maximum level of transparency in terms of model assumptions before making regulatory approvals.

The economics of moonshots: value in rare disease drug development.

Yates N, Hinkel J. *Clin Transl Sci*. 2022;15(4):809-812.

Summary

This article by Yates and Hinkel discusses the economics and associated value involved in orphan drug development. The authors discuss orphan drug development from a historical purview and examine present orphan drug trends, insurance and reimbursement hurdles, value frameworks, and patient-economist perspectives.

Discussion

Value assessment of orphan drugs presents several challenges. These include but are not limited to clinical trials with small patient sizes, lack of clarity on clinical endpoints, lack of existing standard of care for treatment comparison, and nonvalidated quality of life measurement instruments. The authors argue that development of orphan drugs that either cure or positively alter chronic disease conditions should be prioritized, irrespective of the population size affected by the condition. Further, the authors stress the need to place patients at the center of drug development, approval, and treatment decisions. The authors conclude by highlighting that innovative market access strategies would need to be carved out to ensure that patient demand for orphan drugs is met globally despite its increased burden on payers and the healthcare system.

Note from the Section Editor: Views, thoughts, and opinions expressed in this section are my own and not those of any organization, committee, group, or individual that I am affiliated with.

FROM THE REGIONS

LMICs and ISPOR: A Member-Level View

By Christiane Truelove

Health economics and outcomes research (HEOR) is not just for high-income countries. As a global organization, ISPOR strives to support HEOR studies around the world, and has pledged to promote these efforts in lower- and middle-income countries (LMICs) in its Strategic Plan 2024. The Society recognizes that LMICs often face difficulties attaining the financial resources for healthcare spending and are disproportionately impacted by events such as the global pandemic. For these and many other reasons, the organization has long supported HEOR development efforts in LMICs to identify and address barriers to access and budgetary concerns.

In early 2021, a work group [developed a plan of action](#) to evaluate ISPOR's impact in LMICs and improve its efforts. The organization has invested significant resources toward mission-focused initiatives and carrying through those investments into the future. ISPOR's programs to support LMICs include complimentary memberships, fee-waived registrations, and educational grants to enable attendance at ISPOR events. The organization additionally provides complimentary educational webinars, publications, and leadership training. ISPOR global groups also organize activities through regional consortia, networks, and chapters to facilitate information sharing and capacity building.

To see how these efforts play out in practice, ISPOR reached out to members located in LMICs to share their experiences.

The Need for HEOR Programs and the Challenges



Rita Karam, PharmD, PhD is Director of the Quality Assurance of Pharmaceutical Products Program at the Lebanese Ministry of Public Health, Associate Professor at the Faculty of Sciences and Medical Sciences at Lebanese University, and the Program Coordinator of the Professional Master's in "Market Access of Health Products" at the Faculty of Sciences at Lebanese University.

According to Karam, HEOR programs are essential to improving public health, especially in resource-restricted countries. "The aim of every health system is to ensure that the concerned population's health is improved as much as possible. This is definitely not an easy objective," she states. "Additionally, when the resources dedicated for healthcare are relatively scarce, such as the case of Lebanon, the quality of the decisions have an even greater importance, affecting the population at large."

Hampering the healthcare decision-making process in Lebanon is the country's "complicated political dynamic, with a challenging power relations landscape affected at large...by the Lebanese sectarianism," Karam says. At times this has overruled reliance

on evidence in the policy-making process. Other challenges include the "status quo" bias of health system leaders. Despite these challenges, Karam says the Lebanese healthcare system has progressed over the past 2 years, with the clear impact of the civil economic and political crisis.



Alima Almadiyeva, MD, MPH is Deputy Chair of the Salidat Kairbekova National Research Center for Health Development in Kazakhstan and formerly CEO of the Kazakh Agency for Health Technology Assessment. Almadiyeva acknowledges that the political situation in Kazakhstan can make her work more

difficult. As news outlets have reported, at the beginning of 2022, protests against rising fuel prices escalated into antigovernment riots that killed 238 people. And at the beginning of this year, Kazakh President Kassym-Jomart Tokayev dissolved the lower house of parliament and called for snap elections on March 19.

"The features of Kazakh economy are closely tied with political structure and this makes any pioneering steps challenging," she says. "Despite that, we are trying to welcome more specialists into our ranks through education and meetings."

Both Almadiyeva and Karam had particular reasons for going into the HEOR field. For Almadiyeva, her inspiration was a health technology assessment (HTA) implementation project in Kazakhstan in 2011.

"It was a part of a large reform of healthcare that time. I was in charge of the HTA report on hepatitis C treatment, and it was a feeling that I found something relevant for my soul," she says. "As young public health specialists, we did not know much about evidence-based practice and critical thinking because of the huge gap between education at the medical universities and real practice. However, that experience was valuable for me and I did my best to learn and understand the core of the processes involved in HTA production. I understood that evidence can vary, and if you see a meta-analysis it does not mean that it has high-quality evidence, but describes uncertainties which may influence the attitude towards a concrete technology."

According to Karam, she was "driven by the need to rely on solid capabilities contributing to the improvement of the decisions quality...to focus my career on healthcare with a strong commitment and aspiration of improving patient's lives."

The Importance of ISPOR Support

As a cofounder of the ISPOR Lebanon chapter, Karam says one of the main drivers for establishing the chapter is to improve the country's healthcare decision-making process, with the purpose of positively the health outcomes of patients.

"The chapter is still strongly committed to this motto and is pushing for the adoption of several tools for decision making, such as HTA," she says. "ISPOR provides a great support to the country through first, the legitimacy umbrella that is being carefully employed by the chapter, and second, through the wide network—both regionally and globally—enabling a synergy between experts united under one purpose that will better population health."

According to Almadiyeva, "ISPOR opened my mind and motivated me to be who I am. Now, we can easily use all the necessary resources that ISPOR shares with its members. If we have a question that is waiting for a rapid decision, we can find solutions on the ISPOR website with published papers, task forces, updates. It is convenient and free and the knowledge becomes available to use anytime."

"In addition, ISPOR gave me an opportunity to meet intelligent people from each corner of the world and keep in touch with them. In my opinion, this is the most valuable opportunity I have been acquiring for many years, being a part of the ISPOR team."

With ISPOR's resources to draw on, Karam has advocated for HEOR education in Lebanon. As a professor at the Lebanese University and a board member of ISPOR, she helped establish the country's first master's degree program in market access. This program is considered as the first academic initiative. The program offers courses on pharmacoeconomics, pricing, and reimbursement of pharmaceuticals as well as an introduction to all the aspects of HTA.

"My aim is to establish an ISPOR student chapter in Lebanon," she says. "Students are the future of any country and one of the support pillars is to invest in future generations. That's why ISPOR has more than 140 student chapters around the globe." Karam and her colleagues from the ISPOR Lebanon chapter have been involved in teaching courses in their areas of expertise, as well as mentoring and supervising several research projects.

One of the most important ongoing projects that Karam is engaged in is for developing economic evaluation guidelines for Lebanon, in collaboration with the Netherlands' Maastricht University. The project is sponsored partially by the ISPOR Lebanon chapter, since Karam and her doctoral student on the project are both chapter members. "I joined my work as professor at the university with ISPOR, and I think we get a very important outcome deliverable for the country and for the LMICs," she says.

ISPOR and Improving Support

Almadiyeva hopes that eventually her efforts, and those of her colleagues, could establish Kazakhstan's first independent HTA agency. "I opine that we are still working on producing more benefits for Kazakh society—so many issues are not resolved, but I am proud of having colleagues who are motivated like me."

When first getting involved with HEOR and HTA studies, Almadiyeva admits her lack of proficiency with the English language hampered her. "It was difficult to read and understand

professional articles or scientific essays," she says. "Moreover, it was even harder to learn statistics because all advanced techniques are described in English. I would add one more challenge we have been facing for years as non-English-speaking countries, where English is a third or fourth language. The challenge is that the education we had when I just graduated had not been considering an integration with global societies. We were not taught English as a professional language, as well as we did not learn how to think in English."

Even now, she says many resources, new innovations, interesting research, and expert discussions are in English, and Kazakhstan still does not have enough capacity to process that knowledge. "That is a hidden paradox of the situation," she states. "However, there are young generations and we hope that our team will be able to educate young generations to make them competitive on a global level."

ISPOR has provided her with this kind of support. "When I first participated in the ISPOR Conference in 2012, it inspired me to receive those skills I did not have at that time," Almadiyeva says. "I remember how I took part in ISPOR short courses for the first time. Everyone was extremely nice and supported me in discussions. However, I thought that I was an inferior student there because I could not speak and did not understand the full meaning of the topics. When I came back, I started reading and learning more, especially in English."

Although Karam is an advocate for the LMIC work ISPOR has been doing, she adds that clustering countries based on Gross National Income per capita and the World Bank's Atlas method might also overlook major differences between countries.

"What I mean is, clustering countries based on the health system capabilities and resources, in addition to its evolvement status, might be a better idea," she says. "For example, in China, although the World Bank considers China as a middle-income country economy, it has a significantly better capabilities pool and infrastructure when compared to other middle-income countries such as Lebanon and Jordan, for example. And accordingly, I think that clustering these LMIC countries differently might offer better support options or packages, not only from common problems perspective but also from capabilities building and research perspectives."

Acknowledging that there could always be improvements, Karam believes ISPOR is well worth joining. "ISPOR is positioned by most of the healthcare professionals as a highly influential organization with a strong mission statement," she says. "Furthermore, ISPOR is evolving with great flexibility along with new emerging topics in healthcare. We are talking about artificial intelligence, real-world data, value-based healthcare, etc and are remaining relevant to the needs of healthcare system leaders. Thus, the role of ISPOR will definitely continue to grow. I'm confident that joining reaps several benefits—building a great network with like-minded professionals, leveraging on a great learning platform, and staying updated when it comes to meaningful research and trends in healthcare. I think ISPOR is the perfect platform for all these benefits."

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March 15-16 |

10:00AM – 12:00PM EDT

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February 14 | 10:00AM – 11:00AM EST

Preventing, Detecting, and Analyzing Data From Suspected Fraudulent Respondents in Online Surveys, With Examples From Health Preference Studies

What you will learn in this webinar:

- Identify situations where data collection fraud might be a problem in health preferences survey research.
- Learn how to design survey instruments and data collection strategies to reduce the risk of fraudulent respondents.
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February 21 | 11:00AM – 12:00PM EST

Improving Treatment Access and Outcomes by Integrating Social Determinants of Health Data With Real-World Evidence

What you will learn in this webinar:

- Understand the importance of integrating social determinants of health (SDOH) data into real-world evidence generation strategies.
- Learn what data security and privacy considerations are necessary to conduct SDOH- and claims data-linked research in a safe, ethical, and Health Insurance Portability and Accountability Act (HIPAA)-compliant manner.
- Determine the benefits and limitations of linked SDOH-claims based studies in the context of broader evidence generation needs.
- Identify use cases for application of this type of real-world evidence by various stakeholders in the healthcare system.

February 23

10:00AM – 11:00AM EST

HTA Implementation in the MEA Region: An Overview From WHO and Country Updates [HEOR Theater]

What you will learn in this HEOR Theater presentation:


- Understand the update to the World Health Organization's (WHO) health technology assessment (HTA) and benefits package survey.
- Learn from different countries in the region about the status of HTA in their country.
- Receive information about best practices in institutionalizing HTA.

March 31 | 10:00AM - 11:00AM EDT

Health Equity in HEOR: Past, Present, and Future Research Implications

What you will learn in this webinar:

- Identify methodologies and data currently used in health equity research.
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Addressing Assessment and Access Issues for **Rare** Diseases

By Christiane Truelove

In August 2022, the US Food and Drug Administration (FDA) approved Bluebird Bio's Zynteglo (betibeglogene autotemcel), a gene therapy for the rare blood disease beta thalassemia. The drug has a list price of \$2.8 million per treatment, but it's not the first therapy with a multimillion-dollar price tag, and it will not be the last. With the promise of more rare disease treatments on the horizon (particularly genetic treatments for hemophilia and sickle cell disease, which [like Zynteglo] promise to be "one and done" therapies), their much higher per patient cost will create market access and other challenges to payers, providers, and patients.

According to a report by the ISPOR Rare Disease Special Interest Group, the successful development of new treatments for rare diseases and their sustainable patient access requires overcoming a series of challenges related to research and health technology assessment (HTA). Research-related impediments include disease recognition and diagnosis, evaluation of treatment effect, and patient recruitment for clinical research. The primary challenges for HTA for rare disease therapies include a lack of tailored HTA methods, no established standard of care, insufficient knowledge of the natural history of a disease, lack of validated instruments to assess efficacy and effectiveness endpoints, and the application of Institute for Clinical and Economic Review (ICER) thresholds.

In the past, market access issues for rare disease therapies have been mitigated by the size of the population able to be treated, says Darius N. Lakdawalla, PhD, School of Pharmacy at the Leonard D. Schaeffer Center for Health Policy and Economics at the University of Southern California and cofounder and chief scientific officer of Precision Health Economics, a healthcare consulting firm.

With the promise of more rare disease treatments on the horizon, their much higher per patient cost will create market access and other challenges to payers, providers, and patients.

"In that sense, rare disease therapies sometimes faced an easier path than they might otherwise face, but I think that we're reaching an inflection point where that may no longer be the case—or at least will be the case less often. And in particular, I think the advent of gene therapy, or rare disease and other curative types of therapies for rare disease, is forcing that transition."

Methodology of HEOR and HTA Assessment

Traditionally, health economics and outcomes research (HEOR) and HTA methods have been "empirically very bad" at capturing the value of treatments for severe illness and rare diseases because, typically, rare diseases feature high unmet need as the populations are smaller and there is less innovation, Lakdawalla says.

"And it's evident that HTA bodies routinely ignore or make ad hoc exceptions to traditional cost-effectiveness analyses when reimbursing rare disease therapy," he says. "That's a signal to all of us that it just didn't capture the value to payers—let alone patients or beneficiaries—of covering rare disease treatment."

Traditional health economics methods do not account for the "severity premium" in treating illness, according to Lakdawalla,

in that people who are sicker place more value on gains in health than people who are healthier. "It's a very common and intuitive concept from economics, it's sometimes called diminishing returns. It's similar to the notion that someone who lives in a tiny studio apartment values a 500-square-foot addition more than someone who lives in a large mansion in the suburbs. But by the same token, someone who's very ill places greater value on a given health gain than someone who's very healthy."

Translating that to a rare disease, this concept means that the value of health improvement is particularly high for patients with severe illness, and that severity needs to be accounted for. "We now know how to do that in a systematic and mathematically rigorous way, as opposed to just throwing up our hands and trying to guess at what the value should be," Lakdawalla says. "And now I think it's up to a large number of stakeholders to conduct the studies the right way, and to make decisions that reflect the additional value of treating highly severe disease, and that will necessarily increase the value that's ascribed to rare disease treatments."

According to Jennifer Hinkel, MSc, managing director of the Data Economics Company, the HEOR and HTA methodologies learned in school and metrics such as quality-adjusted life year (QALY) and disability-adjusted life year (DALY) "break down" when they are applied to rare disease populations. While this is a known problem and there is work on alternative approaches to these metrics, there has not been widespread academic acceptance of any of them. "I think this is a very open area for research," Hinkel says. "People are probably looking to ISPOR to tell us what to do because we don't know."

"HTA bodies routinely ignore or make ad hoc exceptions to traditional cost-effectiveness analyses when reimbursing rare disease therapy.

That's a signal to all of us that it just didn't capture the value to payers—let alone patients or beneficiaries—of covering rare disease treatment."

— Darius N. Lakdawalla, PhD

The fear in the pharma industry is that the experts coming out of the Institute for Clinical and Economic Review (ICER) with backgrounds at QALY-oriented groups such as The National Institute for Health and Care Excellence will be trying to apply QALY, "which is really a very blunt instrument," Hinkel adds.

Lakdawalla and his colleague, Charles Phelps, have developed an HTA methodology, [GRACE \(Generalized Risk-Adjusted Cost-Effectiveness\)](#), that he says takes methods that have been around for decades, and it fixes an error in those

methods. “Rather than starting from scratch, we started with the methods that are commonly used and addressed an error. The error is, typically, economists have assumed that the value of health improvement is the same regardless of context. So, someone who’s a quadriplegic derives the same value from a modest gain and in function than someone who just has knee pain after running. Most human beings find that to be a completely untenable assumption. And the empirical evidence rejects that too. So, we’ve just addressed that issue.”

The GRACE methodology is not only useful for comparative-effectiveness assessment in rare disease but in cancer, end-of-life care, and disability as well. As Lakdawalla and Phelps write, “Our Generalized Risk-Adjusted Cost-Effectiveness (GRACE) approach helps align HTA practice with realistic preferences for health and risk.”

“The HEOR and HTA methodologies learned in school and metrics such as QALY and DALY ‘break down’ when they are applied to rare disease populations. People are probably looking to ISPOR to tell us what to do because we don’t know.”

– Jennifer Hinkel, MSc

Hinkel believes that patient registries also have a role to play in figuring out rare disease therapy values. “It’s these kind of registry models, where patients are proactively opting in to say, ‘Yeah, I’m willing to have my clinical outcome followed over my lifetime because that’s going to facilitate paying for my therapy. If I change insurers or I change hospitals, I’m willing to be followed and will give you my information and follow-up data in return for getting this paid for,” she says. “I think that will be combined with some financial and reinsurance instruments on the back end that the insurers will have to do.”

Role of Patients in Value Assessment

Annie Kennedy, now chief of Policy, Advocacy, and Patient Engagement at EveryLife Foundation for Rare Diseases, has in the past worked with ICER on assessments for Duchenne muscular dystrophy products, as well as helping the organization refine its algorithm for ultrarare frameworks. “We were really concerned that their framework for just the broad assessment of products was not tailored to some of the nuances in clinical trial development for rare disease,” Kennedy says.

She observes that HTA organizations “have come a very long way” in the past 5 to 10 years in acknowledging the expertise offered. Working with “very well-informed patient advocacy organizations that were doing really sophisticated work and patients who had really relevant experience to bring to bear

now have much more formalized engagement and processes to bring patients and patient communities into the assessment process.”

“I still think we have a long way to go,” Kennedy says. “But we have made progress.”

One of challenges remaining is that there is no formalized mechanism for including patient experience data within regulatory review at the FDA. This means that when companies are preparing dossiers for payers, that information doesn’t get included.

“What I’ve seen all too often is that we will get into an HTA assessment or we will get to a point where we already have a product that’s approved, and now we’re getting to commercialization. We’re seeing policies be issued that are not reflective of engagement with either the clinical experts that are experts in that specific rare disease or patients who have lived experience with rare disease,” Kennedy says. “And then we’re really forced to be playing what I call ‘whack-a-mole,’ where we’re doing one-off conversations with each of the Medicaid plans and each of the commercial plans to bring forward all that data that we have to bear to inform that decision making.”

According to Kennedy, if patient advocacy groups and pharma knew, in a predictable way, what kind of data should have been included, then that data could be developed and included within the clinical trials so that it’s available for consideration. “And that we’re not in hindsight saying, ‘Gosh, that’s compelling to hear that from a patient or a caregiver that burden has been reduced or productivity has been increased. But wow, we wish we had more data published on that.’ If we knew that would be included, that could be collected in a way that would be considered within that assessment or within that algorithm.”

“What I’ve seen all too often is that we will get into an HTA assessment and we’re seeing policies be issued that are not reflective of engagement with the clinical experts or patients who have lived experience with rare disease.”

– Annie Kennedy

In the United States, some of this last-minute scramble for data can be attributed to payers, biopharmaceutical sponsors, and regulators not engaging earlier with patients. “One of the things we do hear from payers is that they find out really too late that a product is coming or is being approved and that there are patient experience data specifically that are

provided to regulators by sponsors that is helping inform their decisions,” Kennedy says. “We would very much like to see that data be made available earlier to payers so that their decisions can be informed also, in the same way that a regulator’s decision is being informed.”

During the 117th Congress, which ended on January 3 this year, EveryLife helped legislators put together the [STAT \(Speeding Therapy Access Today\) Act](#), a bipartisan, bicameral, community-led bill aimed at improving the development of and access to therapies for the rare disease community. The goal of the legislation is to put together a Rare Disease Center of Excellence at the FDA that would serve as FDA’s coordinating office with rare disease stakeholders, implement cross-center rare disease and condition-focused meetings and policy development, and coordinate regulatory science initiatives for rare diseases. The proposal also seeks to enhance coverage of drugs, biologic, and gene/cell-based therapies to treat rare diseases and disorders so payer coverage policies reflect all of the information used by the FDA to determine a drug’s indicated usage and population.

While rare disease advocates have found allies at the pharma companies developing specific rare disease therapies, it is important that “we can also have direct communication with payers, with clinicians, and with each of the stakeholder groups so that we can make sure that it’s the patients who are also

representing their individual experience so that those policies are reflective of patient experience, not necessarily just the priorities of the pharmaceutical company,” Kennedy says.

One example of data left out of access decisions is the impact of a rare disease therapy on caregiver and patient productivity, such as being able to work full time when they could not before or even sleep through the night, or allowing patients to be more independent in their own care, thereby reducing the number of caregiver hours needed. “We conducted a national economic burden of disease study that showed the economic impact of living with a rare disease, which in 2019, was close to a trillion dollars. Nearly 60% of those costs were not direct costs and mark what we consider to be the nonmedical costs,” Kennedy says. “These costs [such as out of pocket and societal] are not the ones that are typically brought into consideration when we think about the traditional health economic models.”

If HTA assessments can go beyond signs, symptoms, functional measures, and biomarkers to include concepts such as pain function, family stress, financial toxicity, and then correlate them to already existing patient-center impacts, “we are going to have decisions that are better reflective of patient values, as well as clinical trial experiences,” she says.

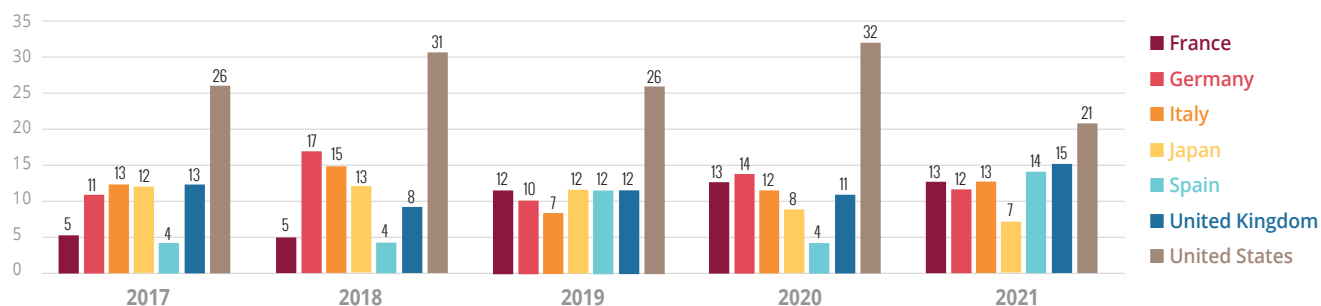
Christiane Truelove is a healthcare and medical freelance writer.

By the Numbers: HEOR & Rare Diseases

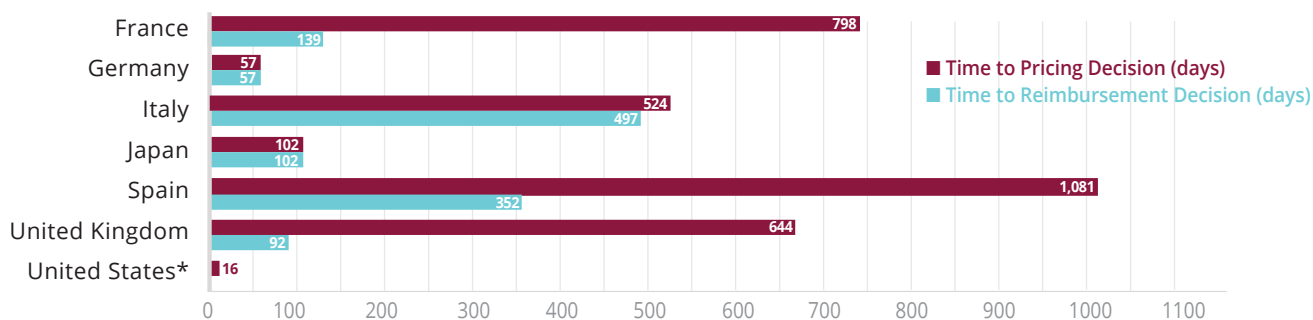
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Number of Orphan Drugs Entering the Market in 7 High-Income Countries



Time to Reimbursement and Pricing Decisions for Orphan Drugs Launched in 2021 in 7 High-Income Countries



*Reimbursement data for the United States was not provided.

Addressing Health Equity in Orphan Disease in the United States: Sickle Cell Disease (SCD) vs Cystic Fibrosis (CF)

3x more people are living with SCD compared to CF



Funding per person affected is **11x HIGHER** for CF patients compared to SCD

1:314

Rates of SCD are higher in Black patients

1:2600

Rates of CF are higher in White patients

7 Effective Market Access Strategies to Accelerate Patient Access to Orphan Drugs

- Conduct innovative, accelerated product development (eg, real-world evidence to complement randomized controlled trials)
- Implement adaptive regulatory pathways (eg, PRIME, priority medicines identified by the European Medicines Agency)
- Generate meaningful patient-relevant outcomes through early and sustained patient engagement
- Engage in early access value demonstration
- Maximize product value from earlier launch to loss of exclusivity using a life-cycle full-spectrum evidence generation strategy
- Differentiate value-based offerings with the greatest net benefit for successful pricing and reimbursement
- Quantify the potential benefits of early access to inform regulators, payers, and health technology assessment bodies.

The Impact of Digital Health Technologies on Health Equity: Designing Research to Capture Patient-Reported Outcomes

Sarah Stothers Rosenberg, RN, MSN, MPH, US Food and Drug Administration, Center for Drug Evaluation and Research, Silver Spring, MD, USA; Brittany B. Carson, PhD, ApotheCom, New York, NY, USA; Amiee Kang, MPH, Bristol Myers Squibb, Lawrenceville, NJ, USA; Ting-Hsuan Lee, MHS, US Food and Drug Administration, Center for Biologics and Research, Silver Spring, MD, USA; Rajshree Pandey, PhD, MPH, Curta Inc, Seattle, WA, USA; Evelyn J. Rizzo, MSc, Lumen Value & Access, New York, NY, USA

Patient-reported outcomes and measures (PROs/PROMs) are increasingly recognized as important tools to evaluate efficacy and safety of interventions from a patient's perspective.

While the growth of ePROs use brings many benefits for data collection, challenges persist and, if not addressed in a timely manner, could contribute to health inequity.

Key considerations for the healthcare community regarding health equity in the development of ePRO/ePROM in clinical research and practice are presented.

Introduction

Patient-reported outcomes and measures (PROs/PROMs) are increasingly recognized by regulators, healthcare providers, and policy makers as important tools to evaluate efficacy and safety of interventions from a patient's perspective.^{1,2} As a result, there is greater recognition of the value of PROs within both clinical research and practice (Table 1).^{1,3,4} With the growing interest in digital healthcare alternatives, like telemedicine and remote clinical trials, we are seeing increased use of ePROs/ePROMs. Also, patients can now increasingly access ePRO systems using their personal devices. This type of electronic patient reporting was very important during the recent COVID-19 pandemic as it allowed for remote access to important patient outcomes, such as remotely monitoring symptoms in oncology patients.¹¹

The COVID-19 pandemic highlighted how social determinants of health

impact health equity.^{7,12,13} It also placed a spotlight on the ripple effect of inequities on healthcare delivery, access, and health outcomes.¹⁴ For example, people with higher incomes are oftentimes more able to work from home, have reduced exposure to COVID-19, and have better internet connectivity allowing for easier access to virtual healthcare, which can translate into relatively better health outcomes versus those with greater social or economic disadvantage(s).¹³

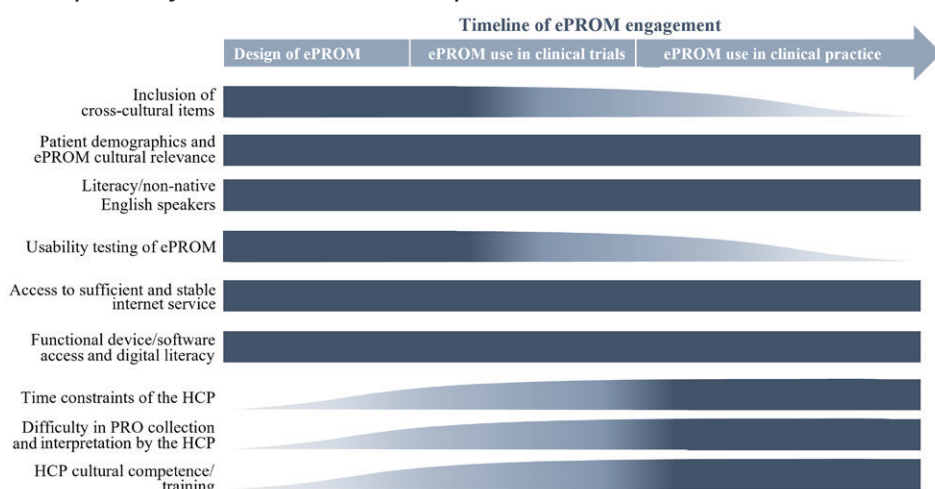
To better address health equity, current healthcare practices and structures should be reevaluated. This includes taking a closer look into the use of ePROs/ePROMs and their impact on health equity and related health outcomes. This article highlights several key considerations for the healthcare community regarding health equity in ePRO/ePROM development as well as operability in clinical research and practice, which are described below and summarized in Figure.

Table 1. Terms and definitions.

Term	Definition
Patient-reported outcome (PRO)	Any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else. ⁵
Patient-reported outcome measures (PROMs)	Tools/instruments used to collect patient-reported outcomes (eg, PROMIS funded by National Institutes of Health). ⁶
Social determinants of health (SDOH)	SDOH are conditions in the places where people live, learn, work, and play that affect a wide range of health and quality-of life-risks and outcomes (eg, build environment, educational attainment, employment). ⁷
Electronic patient-reported outcome (ePRO) ^a	The electronic collection of patient-reported outcome data directly from the patient and/or caregiver. ⁸
Electronic patient-reported outcome measure (ePROM) ^a	An electronic based questionnaire/tool used to collect patient-reported outcomes. ⁹
Health equity	According to the World Health Organization, health equity is defined as "the absence of unfair and avoidable or remediable differences in health among population groups defined socially, economically, demographically or geographically." ¹⁰

^aNOTE: For the purposes of this article, the definitions provided for the above terms were interpreted and developed based on how these terms are used in practice, cited in journals, and used for research purposes. The specific definitions for these terms have yet to be uniformly accepted and/or agreed upon by all stakeholders.

Figure. Key health equity-related considerations across ePROM development and operability in clinical research and practice.



ePROM indicates electronic patient-reported outcome measure; HCP, healthcare provider; and PRO, patient-reported outcome.

Health Equity in the Design of ePROMs

The utilization of ePROMs in clinical trials and practice has increased. This is driven by the electronic design and format that facilitates robust data collection, analysis, and interpretation with fewer errors in comparison to traditional PROMs.^{15,16} While the growth of ePRO use brings many benefits for data collection (eg, expanding our reach to underserved populations), challenges in design of ePROMs persist. If not addressed in a timely manner, these may contribute to health inequity.

For example, some key barriers to implementation of ePROMs identified in the oncology literature include: lack of inclusion of cross-cultural items, limited access to technology, reduced language or literacy, and other psychosocial stressors that contribute to limited usability.¹⁷ People who are socioeconomically disadvantaged, with lower literacy levels, who are non-native English speakers, and/or have a disability may find it difficult to complete ePROMs if they are not designed, translated, or adjusted to account for these factors. Not only do these challenges present barriers to accurate and timely patient input, but they may also increase unnecessary burden on patients and caregivers.^{9,15}

While there is growing interest in the bring-your-own device approach

where individuals use their personal smartphone, tablet, laptop, or other device to complete a measure, users in lower socioeconomic groups may lack access to the latest devices equipped with the operating systems needed to support the platforms used to host the ePROM.^{9,18,19} In addition, lower socioeconomic groups may not have sufficient and stable internet access and their dependence on public internet (eg, mobile hotspots) can prove to be problematic given data security requirements.^{9,15} Potential data breaches when using unsecure internet connections can subject patients and caregivers to privacy risks, which could lead to missing data and generalizability issues that result in inappropriate conclusions.

While the growth of ePRO use brings many benefits for data collection, challenges in design of ePROMs persist. If not addressed in a timely manner, these may contribute to health inequity.

As with conventional PROMs, newly developed ePROMs require content validity and rigorous psychometric evaluation before use (eg, qualitative

evidence and statistical evaluation of instrument validity and reliability). However, in contrast to conventional PROMs, ePROMs also require usability testing to assess the electronic platform/interface.^{5,8,9} Usability testing evaluates the electronic platform for accessibility, security, and privacy.⁸

During the design phase, usability testing of an ePROM and user interface is key in assessing whether the tool is fit for purpose and acceptable to the end user, or the target population.¹⁶ The design must not only consider the domains relevant to the concepts that go into understanding and assessing a disease or condition that are relevant to patients, but they must also consider cultural relevance, age distribution, and other demographic characteristics that may influence outcomes.^{15,20} A careful design that considers these social determinants of health factors, in addition to disease factors, is needed to facilitate the instrument's capture of meaningful data that are applicable to all relevant subpopulations.⁸ For instance, level of education can serve as a proxy measure for assessing literacy level, which is one of the many important components when evaluating content validity and performance of a PROM.

Health Equity and ePROs/ePROMs in Clinical Trials

In clinical trials, ePROMs can provide a comprehensive assessment of the impact of a new intervention on a patient's health-related quality of life through the collection of relevant symptoms and functional impacts that represent the outcome(s) of importance to patients.¹⁹

ePROs/ePROMs can readily capture demographic data that may be relevant to better understand disease heterogeneity, response to an intervention, or the experiences of patients with the disease.^{8,19} ePRO/ePROM data can contribute to real-world data and can be critical in evaluating a therapeutic intervention's value as a part of the totality of evidence in understanding risks or a clinically meaningful benefit.^{2,5,9} This is facilitated by the electronic design and format that enables robust and accurate data collection in comparison to traditional PROs (eg, paper-based instruments).^{15,21}

However, a larger concern with ePROM implementation in clinical trials stems from the lack of racial and ethnic representation and consideration for social determinants of health.² Some key barriers to implementation of ePROMs identified in the oncology literature include lack of inclusion of cross-cultural items, access to technology, language, or literacy, and other psychosocial stressors that contribute to limited usability.¹⁷

Furthermore, although the researchers have the ability to collect more granular data, the data are often analyzed and reported in aggregate to increase the power of the sample.¹⁵ This is likely due to missing demographic or related social determinants of health data,¹⁰ or “sparse data,” that lead to aggregate reporting of results. As a result, the important differences from ePROs that are relevant to various racial and ethnic, or socioeconomic groups may be masked.^{9,22} Lack of careful implementation as well as interpretation of ePROs/ePROMs at the clinical trial level could lead to large generalizations that may have ripple effects elsewhere in the healthcare system.

Many of the ePROs/ePROMs challenges can be addressed in the design phase of a clinical trial (see **Table 2** for resources). Clearly outlined protocols and a statistical analysis plan can mitigate some of the concerns related to ePROs/ePROMs and the role they can play in providing a more holistic picture of patients’ health.

Health Equity and ePROs/ePROMs in Clinical Practice

Despite expansion of ePROs/ePROMs development, their widespread adoption in clinical practice is not fully realized due to technological challenges, workflow inefficiencies, and human factors.³ In clinical practice, ePROs/ePROMs may have direct impacts on the quality of care, access to treatment, and better identification of patients’ unmet needs;²³ in addition to health outcomes and early prediction of disease regression.²⁴ Anecdotal evidence suggests that ePROs/ePROMs can increase completion rates of important assessment measures.¹⁶ They also can serve as an opportunity to detect inequities related to health that may have traditionally gone unidentified.²²

Table 2. Resources and best practices for addressing health equity in ePROs/ePROMs.

RESOURCES & BEST PRACTICES

Critical Path Institute (C-PATH)

Best Practice Documents:

- Best Practices for Participant Registration in Clinical Trials Using Bring-Your-Own Device Technology for Data Collection
- Best Practices for Electronic Implementation of Response Scales for Patient-Reported Outcome Measures
- Best Practices for Maximizing Electronic Data Capture Options During the Development of New Patient-Reported Outcome Measures
- Best Practices for Migrating Existing Patient-Reported Outcome Measures to a New Data Collection Model

ISPOR—The Professional Society for Health Economics and Outcomes Research

Best Practice Reports:

- Wild D, Grove A, Martin M, et al. Principles of good practice for the translation and cultural adaptation process for patient-reported outcomes measures: report of the ISPOR Task Force for Translation and Cultural Adaptation. *Value Health*. 2005;8(2):94-104.
- Patrick DL, Burke LB, Gwaltney CJ, et al. Content validity - establishing and reporting the evidence in newly-developed patient-reported outcomes (PRO) instruments for medical product evaluation: ISPOR PRO Good Research Practices Task Force Report: part 1 - eliciting concepts for a new PRO instrument. *Value Health*. 2011;14(8):967-977.
- Patrick DL, Burke LB, Gwaltney CJ, et al. Content validity: establishing and reporting the evidence in newly-developed patient-reported outcomes (PRO) instruments for medical product evaluation: ISPOR PRO Good Research Practices Task Force Report: part 2 - assessing respondent understanding. *Value Health*. 2011;14(8):978-988.

National Institutes of Health (NIH) Health Equity Research

- <https://www.nih.gov/ending-structural-racism/health-equity-research>

World Health Organization (WHO)

- https://www.who.int/health-topics/social-determinants-of-health#tab=tab_1

US Food and Drug Administration (FDA)

- Digital Health Technologies for Remote Data Acquisition in Clinical Investigations: Draft Guidance for Industry, Investigators, and Other Stakeholders
- Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims: Guidance for Industry
- Patient-Focused Drug Development: Collecting Comprehensive and Representative Input (Guidance 1 of 4 methodological patient-focused drug development guidance documents)
- Patient-Focused Drug Development: Methods to Identify What Is Important to Patients Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholder (Guidance 2 of 4 methodological patient-focused drug development guidance documents)
- Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments: Draft Guidance (Guidance 3 of 4 methodological patient-focused drug development guidance documents)

Alternatively, ePROMs may pose a risk by helping to perpetuate health inequities when instrument evaluation does not include a representative sample population. As with the design of ePROMs, low computer literacy, lack of language proficiency, or limited access to technology may pose challenges due to an individual's capacity to use

or comprehensively interpret and answer these measures, which in turn can impact the later use of ePROs in healthcare management.^{2,15} From the perspective of healthcare providers in oncology, barriers to using ePROMs frequently include limited access to technology and software, time constraints, lack of adherence and

compliance in regular ePRO collection from patients, and difficulty in ePRO interpretation.^{17,25}

To facilitate accurate operability of ePRO/ePROMs, healthcare personnel will need to receive culturally competent training on how to use ePROs effectively in clinical practice. Moreover, when designing and implementing ePROMs, the burden on the healthcare provider or facility must be considered, especially in resource-constrained settings.²⁶ To further support sustainable implementation of ePROs, it is important to install leadership and governance structures within healthcare systems that are adaptable and that support the objectives of diverse healthcare settings.³

ePRO/ePROM data can be used more effectively to improve health equity in healthcare decision making if the results are delivered in a meaningful way to patients/caregivers and their clinical team.

Finally, ePRO/ePROM data can be used more effectively to improve health equity in healthcare decision making if the results are delivered in a meaningful way to patients/caregivers and their clinical team.¹⁹ Research shows that for data to be relevant and actionable, different audiences may prefer alternative ways of communicating and interpreting results.²⁷ Providing ePRO/ePROM information in user-friendly and preferred formats could increase provider uptake and empower patients to be informed and active participants in their own care.^{1,2} Furthermore, dissemination of any subgroup results from ePRO/ePROM analyses should be published along with other key clinical outcomes and/or findings to promote their value for future use.

Discussion and Concluding Remarks

At the core of any healthcare delivery system is the *patient*. With appropriate design and implementation, ePROMs may provide an opportunity to capture relevant sociodemographic information and important outcomes relevant to patients by broadening our reach to

include the underserved populations that may otherwise be missed with traditional PRO data collection.

Despite these advantages, there remains limited evidence regarding the role of ePROs in highlighting health equity issues since much of the health equity data are often underrepresented in medical and health systems research.²⁸ Therefore, it is unclear whether the evidence we have holds true for specific subpopulations. Lack of representation can contribute to an electronic measure that has implicit biases built in that could potentially further perpetuate health inequity.

Opportunities remain in research where appropriate approaches for ePROs/ePROMs design and implementation can be explored. These opportunities include usability testing and the investigation of methods that more comprehensively capture experiences, priorities, and factors associated with social determinants of health. These measures could be a useful tool in identifying and addressing social determinants of health to help reduce disparities in healthcare delivery, access, and health outcomes. Furthermore, ePROs/ePROMs can help us reduce key missing data that may supplement our understanding of a disease or condition from a patient's perspective throughout their healthcare journey. Data from a reliable and valid ePROM for a clinical trial may be used to inform and support clinical practice, payer decisions, drug approvals, and policy decisions.

To fully harness the potential of ePROs/ePROMs, future research is needed to better understand health equity-related data needs as well as appropriate instrument design and implementation strategies for these tools in both clinical research and practice settings.

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Disclaimer:

Sarah Stothers Rosenberg is an employee at the US Food and Drug Administration (FDA) and was a fellow during the development of this article. This article reflects the views of the author and should not be construed to represent FDA's views or policies. Ting-Hsuan Lee was a fellow at the FDA during the development of this article, and as such her contributions are an informal communication and represent her best judgement. These comments do not bind or obligate FDA.

Acknowledgement:

The authors thank Julia F. Slejko, Kathleen Wyrwich, Newell E. McElwee, Ashley Martin, Tan Nguyen, Wai Man Maria Chan, Rinat Ariely, Saara Nasruddin, Caroline Jacobsen, Huda Eldosougi, Ramiro Gilardino, Rebecca Raciborski, Karolina Baloghova, Manan Shah, and Soham Shukla for their contributions to and review of this article.

The Role of Education in Shaping an Open-Source Future

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There is a growing public demand for open science and transparent health policy making.

Open science includes efforts to make scientific knowledge “...*openly available, accessible and reusable for everyone...*, and to open the processes of scientific knowledge creation, evaluation, and communication to societal actors” according to the UNESCO Recommendation on Open Science.

One way to advance both the academic and professional practice of Open Science is to include the development of open science skills within health economics and outcomes research educational programs.

Transparency, Built In

Health policy making is increasingly informed by the results of simulation models. Distrust concerning the results of such models is nevertheless on the rise as their development and underlying methods are often confidential. This contradicts (1) the societal wish for more openness concerning policy making, and (2) the principles of the Open Science movement,¹ which have been steadily embraced by the scientific community. In this article, we focus on the potential contribution of the role of education in developing and using transparent health economic analyses to improve the transparency of health policy decisions, but note that this is not the sole element affecting the transparency of decisions.

While openness is considered valuable from scientific and societal points of view, current health economics and outcomes research (HEOR) education devotes little, if any, attention to training students to perform evaluations adhering to the Open Science¹ or FAIR (Findability, Accessibility, Interoperability, and Reusability) Guiding Principles.² According to the UNESCO Recommendation on Open Science, open science includes efforts to make scientific knowledge “...*openly available, accessible and reusable for everyone...*, and to open the processes of scientific knowledge creation, evaluation and communication to societal actors...”¹ Also, FAIR comprise guiding principles for data management and stewardship that promote the findability, accessibility, interoperability, and reuse of digital assets.²

Today's students will be tomorrow's analysts and policy makers. Hence, the HEOR community should give more attention to developing open-source modeling skills. Future professionals should learn to perform health economic analyses that are transparent, reproducible, widely accessible to all (ideally without restrictions), and interoperable.² Besides modeling skills, this requires the ability to make one's code readable, understandable, and findable by others.

Open science principles¹ also encourage more intensive stakeholder engagement in the practice and communication of HEOR evaluations; these provide a critical means of reinstating trust in science and increasing support for health policy. Existing initiatives within the HEOR community are contributing to this paradigm shift. These include, among others, the Innovation and Value Initiative, the Peer Models Network, the Open Source models Clearinghouse, and ISPOR's Open Source Model Special Interest Group. However, greater visibility and engagement is still needed, particularly with junior HEOR colleagues and students.

While openness is considered valuable from a scientific and societal point of view, current health economics and outcomes research education devotes little, if any, attention to training students to perform evaluations adhering to the Open Science or FAIR principles.

Developing an Open-Source Skillset

Putting the principles of open science into practice requires both technical and social skills. Concerning the technical skills, acquaintance with open source programming languages with high-quality version control, such as Python³ and R,^{4,5} may seem the most adequate medium to prepare future professionals to meet the goals of open science.

Transparency and reusability in modeling can be partially achieved by providing access to source code. Appropriate documentation about a given analysis (eg, inputs, workflows, outputs) and how to modify the model for other purposes allows for peer review. Learning to concisely describe and assess the

underlying theory, assumptions, and variables of models is also critical to participating in open science and should be emphasized in academic curricula.

Exposure to data visualization techniques and tutorials provides means of acquiring open-source skills but learning how to develop and deliver these is also critical to contributing to HEOR's open source future. Interactive data visualization, in particular, can improve public engagement; it is an increasingly important part of health communication in our technologically rich age. The skills to visually represent data and provide interactive or exploratory views of a study should be encouraged among modelers and HEOR scientists. The R package Shiny, for example, supports the development

find a resource that satisfies the needs of a current decision problem, or to publicly share content developed for a specific research question.

Barriers to using existing models may include a lack of documentation, a lack of coding convention, a context-specific design, a lack of validation studies, and confusion around the presence of multiple versions of the model without any curation of each successive release. Researchers may also be discouraged by programs that rely on multiple underlying pieces of code without clear distinctions between what is a functioning or legacy component, or that are written in multiple programming languages. In these instances, a research team may be forgiven for thinking the cost of retrofitting an open-source model is equal to or greater than doing the same to a proprietary model.

The decision to make one's own code open source, while morally admirable and consistent with the spirit of open, peer-reviewed scientific work, also involves barriers. Within HEOR, much of the data used are confidential, personal, or proprietary. In these cases, creating documentation, tutorials, or providing a test sample of data for others to use as proof of concept may be impossible or represent a significant additional resource burden for the developer. The expectation to maintain and update any resource made public, as well as the responsibility to address any potential issues of liability, may also act as deterrents.

The Future of HEOR Open Source

Health economists have drawn attention to the need for a health economic model registry,^{6,7} which would retrospectively and prospectively contain structured information on existing health economic models. This type of platform could address many known problems within HEOR, including the lack of documentation on existing models, the failure to curate open-source model versions, the potential publication bias for proprietary resources, intellectual property disagreements, as well as offer a better way of determining which models or model versions have been subjected to validation studies. In addition, by allowing protocols of health economic models to be cited separately

from journal articles, a more robust conversation about transparency and credibility will be possible.

Improving and assessing existing models is and will remain part of the HEOR community's responsibility to stakeholders and the public. Continuous efforts that address model transparency, validation, and reproducibility already exist, but open-source-specific guidelines and assessment tools will also be needed. Proposed coding frameworks,⁸ checklists such as TECH-VER (Technical Verification)⁹ and AdvISHE (Assessment of the Validation Status of Health-Economic decision models)¹⁰ validation assessment tools all have a place in managing the open-source assets of the future.

Academic programs and training courses in HEOR should incorporate open science and FAIR principles into their curricula. The ability to communicate about, engage with, and contribute to this part of our professional community is an increasingly important and hireable skill. Enhancing transparency and resource availability is consistent with the goals of higher education worldwide. By making graduates literate in programming language including code testing, version control, licensing, distribution, data visualization, and public health communication, we prepare them to be better peers and more effective professionals who can engage with both HEOR stakeholders and the public.

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By making graduates literate in programming language including code testing, version control, licensing, distribution, data visualization, and public health communication, we prepare them to be better peers and more effective professionals who can engage with both HEOR stakeholders and the public.

of apps or dashboards. Alternatively, recorded audiovisual documentation of a study or tutorials for the use of a model can be made available through academic homepages, websites, or social media platforms. Videos or audio annotated PowerPoint presentations can be effective ways to engage with others; they present opportunities to demonstrate a functioning model in real time, to create a dialogue about updates or modifications to an existing open-source resource, or to document the outcomes of an individual analysis for stakeholders and the public.

Limitations of Open-Source Resources

It is important to recognize there are barriers to using existing open-source models. It may not always be possible to

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The Monitor Intervene Predict Value Framework: A Structured Approach to Demonstrating How Digital Health Can Improve Health Outcomes and Reduce Burden of Illness

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Major hurdles will need to be overcome if digital health is to deliver value for all stakeholders (eg, patients, payers, physicians, pharmaceutical companies, and diagnostic/digital device/software developers)

Value attribution will become increasingly important for informing who should pay or be paid (reimbursed), how much, for what, and when

These issues need to be addressed if multi-element “personalized” approaches (involving both digital and genomic technologies) are to enhance the efficiency of healthcare delivery and make disease management more effective

Digital health, by linking patient-level real-world/real-time data—sourced through digital monitoring, interventional disease management, and predictive analytics, together with precision medicine/biomarker informed treatment—is likely to improve economic, clinical, and humanistic outcomes

Healthcare is evolving rapidly. Last year, ISPOR published its “2022-2023 Top 10 HEOR Trends.”¹ These included using real-world evidence in healthcare decision making, value assessment to inform value-driven healthcare decisions, artificial intelligence, and advanced analytics. Complementary research² undertaken by Ipsos indicates that healthcare is becoming more “connected” with multiple components (eg, digital patient-level, real-world/real-time monitoring; software, algorithms, and apps informing interventions; analytics predicting outcomes; and genomics/biomarkers informing therapy choice). In the future, value will increasingly be delivered by multicomponent disease management rather than by drugs or interventions in isolation.

The gradual evolution and fusion of biomarker-informed disease management (eg, genomics/proteomics with companion and complementary diagnostics indicative of disease or treatment response), real-time informed disease management (eg, digital health

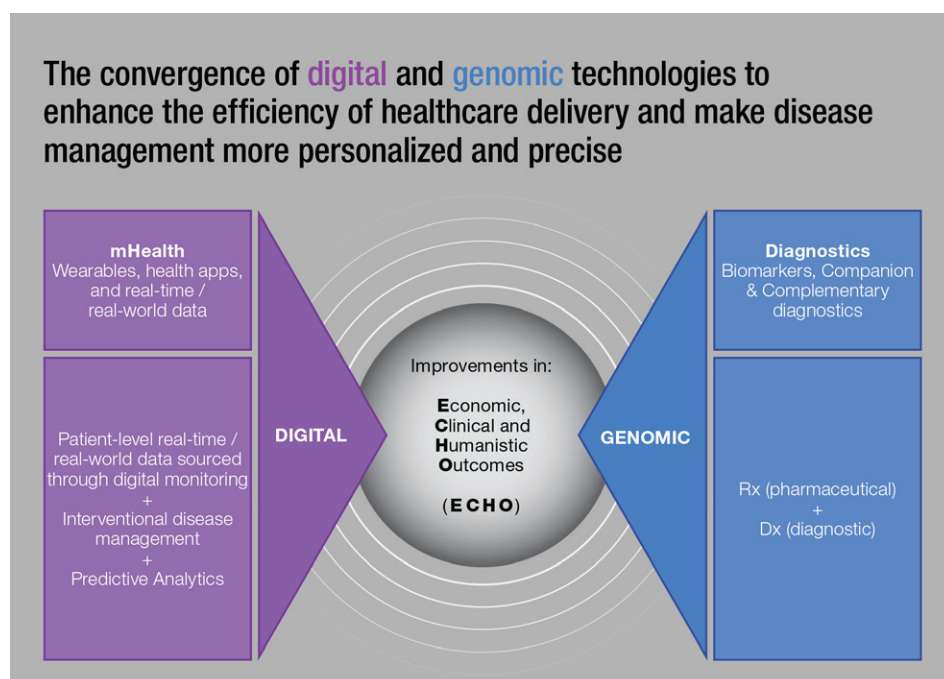
technologies and wearables), and intelligent smart disease management (eg, advanced analytics, software, algorithms, and artificial intelligence), with all components having both diagnostic and predictive elements, is opening up opportunities to enhance the efficiency and effectiveness of healthcare delivery by making treatment more personalized and precise (Figure 1).

This will create challenges for value, price, and health technology assessment and will require new approaches to value evidence generation and value attribution. Of increasing interest are digital health technologies addressing monitoring, intervention, and prediction (see left-hand side of Figure 1).

The first challenge surrounds speed of evolution

Technology is evolving faster than the regulatory, behavioral, healthcare funding, and health technology assessment (HTA) systems that are required for successful implementation.

Figure 1. The convergence of digital and genomic technologies



For digital health to deliver on the promise, developers will need to produce relevant robust evidence regarding the technology for assessors; systemic changes will be required in regulatory and HTA assessment systems; the roles of the physician and data in disease management, payment systems, and the pricing of healthcare will need to change (Figure 2).

The second challenge surrounds evidence

There are various challenges to evidence development in this environment, including:

- relevance, robustness, and rigor
- difficulty and cost of evidence development
- timeliness of evidence delivery
- continued validity of evidence in a rapidly evolving environment
- measurement and attribution of codependent value between developers of the different disease management components.

Evidence development will increasingly depend on input from all stakeholders. Responsibility will, however, depend on the nature of the challenge. Funding of evidence development (fully or in part) may be the responsibility of the manufacturer, whereas attribution of value (linked to reimbursement) may be the responsibility of the payer.

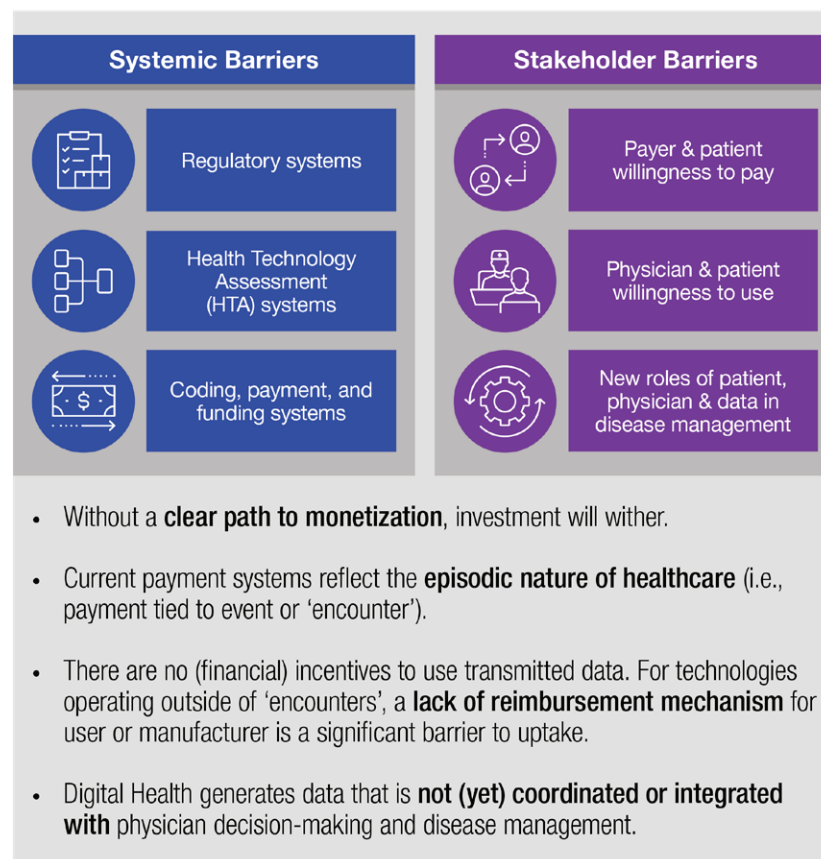
One approach to delineate how much or what kind of evidence is needed is to apply a functional classification of digital health technologies. Classifying digital health technologies by function allows them to be stratified into evidence tiers (typically A, B, C). The evidence level needed for each tier is proportionate to the potential risk to users from the digital health technologies in that tier.

Under current NICE guidance³ in England, for example, the evidence tiers are as follows:

• Tier A: System impact

- system services: digital health technologies with no measurable patient outcomes but which provide services to the health and social care system

Figure 2. Barriers to delivering the promise of digital and genomic technologies



• Tier B: Understanding and communicating

- inform: provides information, resources, or activities to the public, patients or clinicians; includes information about a condition or general health and lifestyle
- health diaries: includes general health monitoring using fitness wearables and simple symptom diaries
- communicate: allows 2-way communication between citizens, patients, or healthcare professionals

The most relevant to future digital/wearable technologies, **Tier C involves monitoring, intervention, and prediction elements**. Tier C interventions typically include:

- preventive behavior change: address public health issues like smoking,

eating, alcohol, sexual health, sleeping, and exercise

- self-management: allows people to self-manage a specified condition; may include behavior change techniques
- treatment: provides treatment; guides treatment
- active monitoring: using wearables to measure, record, or transmit data about a specified condition; uses data to guide care and intervention
- calculation: a calculator that impacts treatment, diagnosis, or care
- diagnose: diagnoses a specified condition; guides diagnoses
- prediction: indication of the likelihood of an event occurring based on monitoring and intervention

For Tier C interventions, best-practice evidence standards include:

- **high-quality interventional study** which incorporates a **comparison**

group, showing improvements in relevant outcomes, such as:

- **patient-reported outcomes** including **symptom severity** or **quality of life**
- other clinical measures of **disease severity** or **disability**
- healthy **behaviors** and physiological measures
- **user satisfaction and engagement**
- health and social care **resource use**, such as admissions or appointments.

There are, however, limitations and barriers for success to this approach. For example, a reluctance to develop evidence by the manufacturer of the digital health technologies, which may be caused by issues of feasibility, affordability, and risk. In addition, a reluctance of the healthcare system to adopt and fund the digital health technologies, which may be caused by issues of infrastructure. Current payment systems reflect the episodic nature of healthcare (ie, payment tied to an event or “encounter”). For many digital health technologies that operate outside “encounters,” there is no mechanism to reimburse the user or the manufacturer.

The third challenge involves the assessment and attribution of value

Value frameworks are becoming increasingly useful and important for structuring the value of multicomponent

disease management. Although traditional payers still focus on economic, clinical, and humanistic outcomes, they anticipate that—driven by advances in digital health and a shift in costs and healthcare responsibility onto patients—this will need to evolve with value being analyzed in different ways⁴:

- **value contribution** of 3 different elements: Monitoring, Intervention, and Prediction, MIP paradigm
- **value segmentation** based on 3 outcome types: ECONOMIC, CLINICAL, and HUMANISTIC
- **value perception** based on 3 stakeholder groups: PATIENT, PAYER, and PHYSICIAN
- **value attribution**, informing value-based reimbursement allocation, will become increasingly important as multiple stakeholders (eg, drug, diagnostic, and device manufacturers; software and app developers) become involved in more holistic disease management. This will be needed to inform who pays/is paid (reimbursed), how much, for what, and when.

Payers see value in all elements of the MIP paradigm but see potential ethical, legal, and regulatory challenges emerging from an intervention element that is driven by automated analytic algorithms/machine learning/artificial intelligence, rather than “traditional” healthcare provider-driven decision making. Ethical

and legal challenges may arise from the question of where responsibility lies for the consequences of decision making around interventions such as dosage or therapy change. Regulatory challenges may relate to the balance between risk and benefit.

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