

VALUE & OUTCOMES SPOTLIGHT

A magazine for the global HEOR community.

Global Price Transparency

- 5 A Way Forward for ATMPs
- 29 Payer Perceptions of Nonclinical Value Drivers
- 32 Do We See the Complete Picture of Pharmaceutical Prices?
- 35 International Perspectives on Price Transparency



VALUE & OUTCOMES SPOTLIGHT

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TABLE OF CONTENTS

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

FROM THE EDITOR

- 3 Can Equitable Access Be Achieved With Global Price Transparency?

ISPOR CENTRAL

- 4 HEOR News
- 5 *Signal: A Way Forward for ATMPs: How Pharma, Payers Can Determine Value-Based Assessments*
- 9 From the Journals
A scoping review of the use of machine learning in health economics and outcomes research: part 1—data from wearable devices and part 2—data from nonwearables
- 11 Research Roundup
- 12 From the Regions
Making an Impact: ISPOR Outstanding Chapter Award 2022
- 14 Conferences, Events, Education, and Resources

FEATURE

- 18 No Clear Answers for Transparent Drug Pricing
- 21 By the Numbers: Global Price Transparency

HEOR ARTICLES

- 22 Equitable Access to COVID-19 Vaccines in the United States: An Overview of the Evidence-Based Recommendations and Evaluation of the Outcomes
- 25 Socioeconomic Influences on County-Level Differences in COVID-19 Incidence During the Second Wave in Germany
- 29 Payer Perceptions of Nonclinical Value Drivers
- 32 Distribution Markups and Taxes for Prescription Pharmaceuticals: Do We See the Complete Picture of the Pharmaceutical Price?

Q&A

- 35 International Perspectives on Global Price Transparency
An Interview with Alexander Roediger, MA and Leandro P. Safatle, BS

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FROM THE EDITOR

Can Equitable Access Be Achieved With Global Price Transparency?

Access to affordable medicines continues to be a challenge due to pricing and reimbursement policies. Global price transparency and its impact on equitable access are issues that have been widely discussed. Many agree that global price transparency is not just about the price of drugs but more about the added value or benefit the innovative therapy brings to patients in different settings, including in low- and middle-income countries (LMICs).

High drug prices present a significant challenge for LMICs as well as developed countries. When it comes to patient access to innovative therapies, manufacturers are the first to be blamed for the high drug prices as a major barrier to patient access; however, it is not that simple. We must look deeper into the policies and processes in countries to understand health economics drivers and how pricing works in the industry. For example, in the United States, multiple innovations and therapies are available but if patients cannot afford them, then those innovative therapies will not improve patients' lives. PhRMA reported that in 2021 there was an average price increase of only 1.0% for the branded medicines that health plans paid due to negotiations. However, patients continue to feel the burden as these health plans and pharmacy benefit managers (middlemen) have shifted more healthcare costs to patients through coinsurance and high deductibles. Unlike services for hospital stays and physician visits where health plans often share the costs with patients, this is usually not the case for medicines. Patient spending on branded medicines for commercially insured patients is often based on the undiscounted prices (list price) rather than the negotiated discounted prices (net price) health plans receive, leading to patient out-of-pocket costs for branded medicines increasing by 50% since 2014 according to PhRMA. To address the issue of patient access, we need to look at this holistically and reshape the insurance system to ensure these savings are passed on to patients.

As Dr Jens Grueger points out in this issue's feature article, two areas should be examined when it comes to price transparency: (1) the confidential tendering and commercial contracting process, and (2) the use of reference pricing. Commercial confidential contracting has its own clear process yielding optimal prices. Disclosing these rebates could lead to price convergence toward an average price band that applies to all. High-income countries could benefit as the price would be lower than what they can afford. On the other hand, LMICs would not benefit as the average price would be higher than what they can afford, leading to longer patient access delays.

Use of international price referencing for new innovative therapies with patent protections makes sense but only when a group of countries are economically similar. The concern arises when countries that are very different economically are grouped as the price convergence would yield the lowest prices in that group of countries and, metaphorically, would be like comparing apples to oranges. The goal is to make these products available globally to address an unmet need, including LMICs where affordability issues is a concern.

Differential pricing (pricing based on affordability levels) may be a path forward and has clearly been demonstrated in HIV/AIDS. Stakeholders, including manufacturers and governments, cooperated and agreed to pricing these treatments based on what countries could afford to pay (in the case of LMICs, at a fraction of the price of high-income countries). This improved global patient access and addressed the issue of affordability.

The HIV/AIDS area clearly demonstrated that affordable patient access is possible, but it will take all stakeholders working together to improve patient access to innovative therapies. This will also require an acceptance of an agreed framework allowing for confidential rebates and eliminating external reference pricing.

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



HEOR NEWS

1 Thousands of Experts Hired to Aid Public Health Departments Are Losing Their Jobs (KHN)

The majority of the Centers for Disease Control and Prevention Foundation's contracts for about 4000 epidemiologists, communication specialists, and public health nurses—hired to help understaffed local health departments during the COVID-19 pandemic—are about to expire, leaving these departments to deal with a possible winter uptick in COVID cases, the ongoing threat of monkeypox, and other public health issues.

[Read more](#)

2 Depression, Panic Disorder Fester in Korea as Social Stigma Persists (The Korea Herald)

In 2021, 256 people between the ages of 10 and 20 years took their own lives, with suicide being the number one cause of death of people under 30. These figures indicate that growing number of young people in Korea are suffering from mental illness, but social stigma prevents them from getting help.

[Read more](#)

3 New Behavioral Science Guide Set to Help Policy Makers With Public Health (National Health Executive)

Public Health Wales and the University College London's Centre for Behaviour Change have laid out a framework that can help public health policy makers and decision makers use the principles of behavioral health to increase the chances of getting their desired outcomes.

[Read more](#)

4 AstraZeneca's COVID-19 (Mis)adventure and the Future of Vaccine Equity (BMJ)

Robert Fortner writes about what went wrong in AstraZeneca's nonprofit partnership with Oxford University in developing the latter's COVID-19 vaccine, and the implications for future vaccine development, especially for lower- and middle-income countries.

[Read more](#)

5 To Start Rebuilding the COVID-19 Safety Net, Amend the 340B Drug Discount Program (Health Affairs)

With the ongoing public health emergency of COVID-19, Mika K. Hamer, Kelsey M. Owsley, and Lindsey E. Fish say the Health Resources and Services Administration should revise the 340B policy to allow eligible entities to buy therapeutics with emergency use authorization for the treatment of COVID-19.

[Read more](#)

6 African Region Tops World in Undiagnosed Diabetes: World Health Organization Analysis (WHO)

The World Health Organization study found that only 46% of people living with diabetes in the African region know their status, with some of the barriers to testing being lack of testing facilities and equipment, inadequate number of trained health personnel, poor access to health facilities, and lack of awareness about diabetes.

[Read more](#)

7 Nigerians Trade Waste Material for Health Insurance (Zawya)

With only 3% of Nigerians having health insurance, Soso Care's program allows people who do not have enough money to see a doctor to get healthcare coverage by collecting and turning in waste material such as plastic and used car batteries.

[Read more](#)

8 Sidra Medicine Study Reveals Genetic Map of Arab and Middle Eastern Populations (Middle East Health)

The high-resolution map of the genetic structure of Arab and Middle Eastern populations published in *Nature Communications* may lead to greater strides in precision medicine tailored to these groups.

[Read more](#)

9 Diabetes Cases in the MENA Region to Increase to More Than 135 Million by 2045 (Zawya)

Cases are being driven by unhealthy eating patterns based on increased income and urbanization, lack of physical activity, and less emphasis on nutritional education.

[Read more](#)

10 Children to Be Screened for Diabetes Risk in United Kingdom Early Detection Trial (The Guardian)

The study, dubbed Elsa (Early Surveillance for Autoimmune Diabetes), will be looking at 20,000 children between the ages of 3 and 13 years to determine their risk of developing type 1 diabetes and detecting it at the earliest state possible.

[Read more](#)



Signal IN BRIEF

- Advanced therapeutic medicinal products (ATMPs) present groundbreaking ways of treating disease, but also groundbreaking challenges related to the use of adequate evaluation methods, sustainable payment models, and organizational conditions to enable the uptake of these treatments.
- ATMPs require high upfront costs for public healthcare providers, due to new logistical and infrastructural demands such as investments in infrastructure (equipment, storage, and treatment capacity) as well as more complex procedures for quality control.
- In a real-life example of how a contract for an ATMP can be negotiated, Novartis, the Danish Medicines Council, and Amgen, the buyer for all of Denmark's hospital medicines, came up with a value-based agreement for a gene therapy medication.

A Way Forward for ATMPs: How Pharma and Payers Can Determine Value-Based Agreements

For public decision makers, advanced therapy medicinal products (ATMPs)—medicines for human use based on genes, tissues, or cells—offer groundbreaking new opportunities for the treatment of disease and injury, but their complexities also present groundbreaking challenges related to the use of adequate evaluation methods, sustainable payment models, and organizational conditions to enable the uptake of these treatments.

Even before the first patient is treated, ATMPs require high upfront costs for public healthcare providers due to new logistical and infrastructural demands such as investments in infrastructure (equipment, storage, and treatment capacity) as well as more complex procedures for quality control. This is more than just the list price for these medicines, which are often very high. “In the last couple of years, we have seen list prices up to 2 to 3 million euros for treatment for some of the new gene therapies,” says Sarah Wadmann, PhD, senior researcher at the Danish Center for Social Science Research – VIVE. “And in addition to the cost of the medicine, there are also significant investments that need to be made to enable the use of these therapies.”

On top of the costs, the long-term clinical effectiveness (especially for so-called “one-time” treatments)—as well as any adverse effects—are unknown. “Typically, the timeframe of clinical trials is not long enough to capture long-term effects,” Wadmann says. “And the smaller patient populations can make it difficult to make adequately powered randomized controlled trials. So for payers, it’s challenging to determine if these therapies are cost-effective, and even if they are, how to ensure affordability and patient access given the budget impact.”

Many countries are already under strain when it comes to drug spending. According to a new report from the Oslo Medicine Initiative in 2022, medicines (excluding drugs used in hospitals) accounted for 17% of total health expenditure on average in EU countries in 2016. Yet the proportion was more than 40% in Bulgaria, more than 30% in Romania, and more than 25% in Latvia, Lithuania, Greece, Hungary, Croatia, and Slovakia. “For payers, especially in lower- and middle-income countries, it’s a real concern if expenditure on new medicines outpaces the growth of other healthcare expenditures,” Wadmann says.

According to Wadmann, trying to determine the value of ATMPs has reopened some classical valuation debates, such as what counts as valid evidence for clinical effects, and how to account for other types of effects than direct health effects (eg, productivity gain). Regulators, health technology assessment agencies, and manufacturers need to find out how to deal with observational study designs and real-world data, as well as discounting—that is, determining the value of effects that will only materialize in the future.

While these valuation issues are not exclusive to ATMPs, to overcome the challenges, pharmaceutical companies, public authorities, healthcare payers, and other stakeholders

must develop joint solutions. “International coordination is key because evidence production in the pharmaceutical sector is often planned on a global scale,” Wadmann says.

Denmark and one of the first outcomes-based agreements in gene therapy

Public healthcare providers can look to a real-life example of an ATMP valuation approach in Denmark. The Danish Medicines Council and Amgro, the buyer of medicines for Danish public hospitals, were able to collaborate with Novartis to generate an innovative outcomes-based pricing agreement for a gene therapy medication.

What helped in the beginning of the journey to determine the valuation of this product was that Denmark already had a registry for patients with hereditary eye diseases, according to Pia Krogsgaard Villadsen, MBA, head of market access for Novartis Denmark. At the time, 12 patients were diagnosed and found eligible for treatment. “That means that the patients were actually already set up for the entrance of this gene therapy into the Danish market,” Villadsen says. “That’s important to remember, because that obviously has an impact on the initial high budget impact when you talk about this treatment.”

Novartis submitted the dossier for the medication to the Danish Medicines Council in March 2019, and then did the price negotiations with Amgro after the added value assessment by the Council. These negotiations “were tough,” Villadsen says. “I must admit tougher than normal for more standard products.”



“For payers, especially in lower- and middle-income countries, it’s a real concern if expenditure on new medicines outpaces the growth of other healthcare expenditures.”
— Sara Wadmann.

In September 2019, the Danish Medicines Council issued its first rejection for the therapy, raising concerns related to the durability of the gene therapy, and what the council stated was “an unreasonably high price,” according to Villadsen. “So it was back to the negotiation table, where we sat down for many meetings and discussions, and really tried to dig deeper to try to better understand the concerns from payers.”

Finally, on April 27, 2020, the Danish Medicines Council gave its endorsement after finalization of the negotiations on a pay-for-performance agreement. One of the critical success factors was the identification of an objective efficacy measure to build the agreement on, one actually used by ophthalmologists in clinical practice. “We decided on a success criteria for the efficacy—if we reached that, the payments would continue over a period of years, but if we didn’t hit this threshold, the subsequent payment installments would stop,” Villadsen says. “That was an attempt to both address the durability concern, but also to spread this initial high budget impact over several years.” There was also the desire from Amgro and the payers to design an agreement that could be used as a template for other disease areas as well.

Trying to hammer out the contract was essentially starting “almost from the beginning,” says Dorte Bartels, MSc, MBA. “Again, we need to do it a little bit different than we normally do because we need to involve many more people than we do in a regular contract for a product,” says Bartels. Negotiation had to include stakeholders in the region and in the hospitals, as well as the medicines council, Amgro, and a pharmacist.

All of the negotiations resulted in a 120-page contract instead of the typical 20-page Amgro contract, Bartels says, adding that the process was “very huge, and very complex, but we learned a lot.” She adds that even though the contract was very complex to negotiate, both sides tried to simplify at least the patient data collection part of it, agreeing to “keep it as simple as possible” to collect and analyze what was needed to determine the outcomes.

Villadsen says on the Novartis side, one of the learnings was that it was important to start a dialogue early with payers, even before having all the clinical details about a therapy in hand—“even though it’s just at a conceptual level.”

“Before you put a proposal for an agreement on the table, you need to understand the concerns from the payers—both the formal ones, and the informal ones,” Villadsen says, adding that the company made the mistake of being “too quick” in offering a proposal to the Danish Medicines Council and Amgro. “When we got the first rejection, it left us frustrated, but especially also the physicians and the patients” who were waiting for the therapy to be approved.

But one of the things that made the negotiations ultimately successful was that the parties managed to agree on an efficacy measure, one “that was completely objective, not open for interpretation or disagreement,” Villadsen says. And having a patient registry already in place helped, “because from day one you can already monitor the patients and include the efficacy data for each individual patient in the registry.”

Bartels agrees that companies who want to get their ATMPs approved need to start talking earlier with payers. “And it will be very, very useful for us to have the experience...[to learn] about what’s happened in other countries around us...[and discover whether] a company has tried this before?” she says.

On Amgro’s side, “We need to do it a little differently in the future when we have these ATMPs,” Bartels says. “We have started to make a new standard contract for ATMPs, where we involve all the people in our back office—and by that, I mean that the pharmacies, the departments, the lawyers in the regions—we have checked all of these into a consultation.”

Within the next few months, Amgro is hoping to have an ATMP contract template on its homepage “so everybody can see what we are thinking should be a part of an ATMP, and what could a contract look like,” Bartels says. “Hopefully, we can have a system where we can do it in a much easier and less time-consuming way.”

Denmark’s experience with negotiating an outcomes-based agreement for this gene therapy medication showed that when it comes to negotiating ATMPs, payers and pharma can work successfully together, Bartels says, “because we both, on both sides of the table, would like this to be a success, so the patient in the end could have the medicine.”

ISPOR’s *Signal* series

Wadmann, Villadsen, and Bartels spoke about ATMP valuation and contract negotiations during ISPOR’s 8th *Signal* installment, “New Insights Into ATMP Valuation and Outcomes-Based Pricing Experience.” ISPOR started the [Signal program](#) to bring a broader understanding of innovation (beyond product innovation), with the goal of putting these issues front and center for the health economics and outcomes research (HEOR) community. Each episode in a series is a self-contained installment and not dependent on the previous episodes; however, all are connected by an intent to look at the concept of innovation and experience with it from

“Before you put a proposal for an agreement on the table, you need to understand the concerns from the payers—both the formal ones and the informal ones.”

— Pia Krogsgaard Villadsen

“...we both, on both sides of the table, would like this to be a success, so the patient in the end could have the medicine.”

— Dorthe Bartels

different groups of healthcare stakeholders, building foresight into how these innovations might impact healthcare decision making in the next decade.

The first *Signal* program, “[Next Gen Innovation: ‘How To’ From the US Department of Veterans Affairs](#),” highlighted how the US Department of Veterans Affairs’ ecosystem has emerged as a model for supporting the entire life cycle of innovation in a large and highly complex integrated health system. ISPOR’s second *Signal* series event, “[From Price Determining Value to Value Determining Price: It’s About Strategy at a System Level](#),” looked at how to bring systems-level thinking to healthcare and how the pharmaceutical industry, payers, and HEOR experts can work together in a new system for commercial strategy. The third *Signal* event, “[National Institute for Health and Care Excellence \(NICE\), UK: Transformation in Action](#),” looked at how NICE intends to be at the forefront of anticipating and rapidly evaluating new and existing technologies to provide independent, world-leading assessments of value for the UK’s National Health Service and improved access for patients. The fourth *Signal* event, “[Venture Capital Investment: Upstream Decision Making on Value in Healthcare](#),” examined how innovation in healthcare—from therapies to research on the best care protocols—is funded before concrete solutions come to the market, and how that paradigm can change. The fifth episode, “[The New Science of Cause and Effect: Causal Revolution Applied](#),” addressed the challenges of causal models spanning the subjects of selection bias, personalized treatment effect, fusion of data from several sources (observational and experimental studies), and causality in observational studies as well as application of modern computing tools in HEOR. The sixth installment in the *Signal* series, “[New Analytical Approaches to 21st Century Challenges](#),” focused on envisioning and discussing the approaches needed to analyze the many, often irrational-seeming, behaviors that are generated by the myriad

interactions of billions of people, firms, and institutions locally or globally, in small groups or as nations, at timescales ranging from nanoseconds (as in computer trading) to millennia (as in evolution). ISPOR’s seventh *Signal* installment, “[The Real Experience Revolution®: Towards a New Empiricism of Health](#),” welcomed Christopher Lawer, creator of Umio and the Umio Community, who presented a new “radical” empiricism of health and its interactional creation, and explored how we can better see real experiences with health, disease, and illness; ask how and why do real experiences form, become different, and recur; and address the origin and persistence of health inequalities and disparities within social groups, places, communities and populations.

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KEY TAKE-AWAYS

- Contracts for ATMPs are much more complex to negotiate than contracts for standard medicines, due to the uncertainty of long-term clinical effects, the high costs, and the logistical requirements related to production, transportation, storage and administration of the therapies.
- The existence of a registry in Denmark for the patients having the type of eye disease that the gene therapy medication can treat helped both sides figure out how many would be eligible for the drug. Additionally, the registry gives a way to track the efficacy and adverse effects—data essential for the value-based agreement.
- Novartis was able to determine an efficacy measure to build the contract on, which determined the success criteria for payments.
- Starting a dialogue early on between pharma and payers is critical, but a contract should not be offered until all of the payer’s concerns are thoroughly understood.
- Denmark plans to use the agreement with Novartis to make a template for other ATMP agreements. This template would also help manufacturers understand what should be in an ATMP contract.

FROM THE JOURNALS

A scoping review of the use of machine learning in health economics and outcomes research: part 1–data from wearable devices and part 2–data from nonwearables

Lee W, Schwartz N, Bansal A, et al. *Value Health*. 2023;26(1):article in press; and Lee W, Schwartz N, Bansal A, et al. *Value Health*. 2022;25(12): 2053-2061.

Artificial intelligence and machine learning techniques and their use in healthcare and health economics and outcomes research (HEOR) have been touted as the next big game changer, and applications have popped up in various HEOR areas recently (eg, for use in automatic literature screening for systematic literature reviews, as well as its use in analyzing real-world data to support market access for products). To aid the understanding of the use of machine learning (ML), the [ISPOR Good Practices Report guidelines](#) outlined areas where ML could enhance current research (Figure 1).

The guidelines provide use cases for each application; however, the current status of ML techniques in HEOR has not been comprehensively described. A team of researchers have reported 2 scoping reviews to provide a picture on the use of the ML techniques in HEOR and reported them separately for wearable devices and nonwearables.

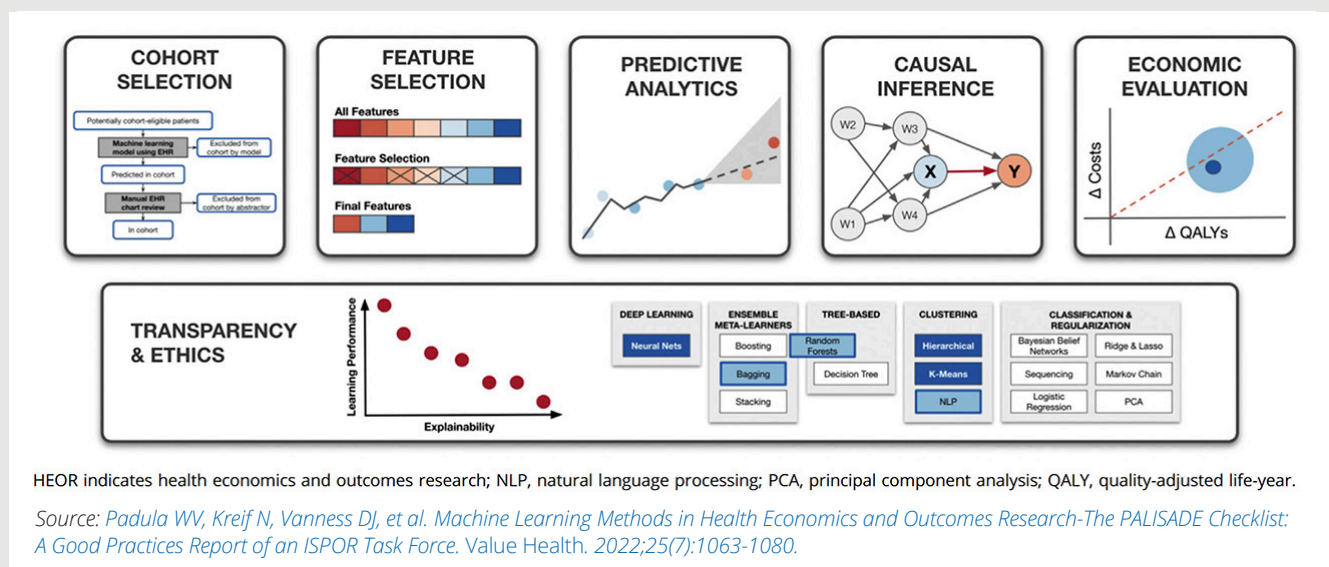
Main inclusion criteria for the review were the use of an ML technique and an HEOR-related topic, with the latter defined as “focusing on the clinical and economic aspects of health or health interventions.” The review on wearables included the period between January 2016 and March 2021, and considered data from wearable devices (with wireless mobility, wearability, and portability that could include smartphone data), while the nonwearable literature included the period between January 2020 and March 2021. Note that wearables specifically designed for clinical purposes were excluded (eg, continuous glucose monitors).

Both reviews used standard systematic literature review techniques for the search, screening, and data abstraction. They extracted similar information about the ML techniques used (type, outcome variables, performance metrics) and different outcomes for Parts 1 and 2. For wearables, (1) types of wearable devices, (2) types of data measurement (eg, episodic or longitudinal) and (3) the number of observations in the training dataset were reported. For the nonwearable review, (1) disease areas, (2) application purposes, (3) types of model outcomes, and (4) application settings were reported (Table).

In terms of the ML techniques applied, both studies found that tree-based models (25% to 31%), and support vector machine approaches (14% to 19%) were most frequently applied—arguably the simplest and oldest ML methods. This may be driven by the ease of use of these approaches and the high importance of relatively easy interpretability in medical research, as opposed to model goodness of fit. Complex ML algorithms like Bayesian networks and super learner methods were much less frequent.

Apart from the techniques, goals of applications were diverging. Unsurprisingly, analyses of data from wearables focused on monitoring general health, while nonwearable studies had a goal of forecasting disease-specific outcomes based on data from electronic medical records. Forecasting with wearable data was rare and mostly published between 2019 and 2021.

Figure 1. Conceptual Diagram of Machine Learning Applications in Health Economics and Outcomes Research



The insight the pair of scoping reviews provides is that ML applications are still limited in HEOR applications. The authors point out future directions that may change that, including greater availability of linked data sources and ML applications on randomized clinical trial data. For wearables, their capacity to provide an alternative to self-reporting, questionnaires, and clinical visits, and the capacity of routinely collected nondisease specific metrics to signal progression (psychological stress on cancer, sleep patterns for neurodegenerative disease) are future directions of research.

The papers along with the ISPOR Good Practices Report on ML methods (Padula et al, 2022) provides the conceptual diagram of ML applications provide readers an excellent guidance into ML methods in HEOR. Future work will be required to evaluate the transparency of the analyses using ML for decision makers and more detailed assessment of the benefits of their use.

Table. Summary Findings

	Part 1: Wearables	Part 2: Nonwearables
Included studies	32 studies included	92 included studies
Model count/ performance metric count	72 ML models 66 model performance metrics	210 ML models 236 model performance metrics
Top 2 ML technique	Tree-based (31%) Logistic regression (18%)	Tree-based (25%) Support vector machine (19%)
Topic	Mostly nondisease specific	Mostly disease specific
Goal of ML application	Monitoring (78%) Forecasting (22%)	Monitoring (14%) Forecasting (86%)
Outcome	General health (24%) Physical activity (22%) (see Figure 2 below)	Clinical event or disease incidence (42%) Treatment outcomes (22%)
Data source	40% smartphone/watch 60% from device with medical purpose (strap sensors, ECG device)	35% EMR data 23% primary data collection 15% registry data

ECG indicates electrocardiogram; EMR, electronic medical record; ML, machine learning.

Figure 2. Nonwearables: Types of Model Purpose and Outcomes (n=32)

Model outcomes	Goal of application			Examples of model outcomes
	Monitoring	Forecasting	All	
General physical or mental health	6 (18)	2 (6)	8 (24)	General wellbeing, ³³ biological age, ³⁸ stress or mental fatigue, ^{43,47} physical functioning ³²
Physical activities	7 (22)	0 (0)	7 (22)	ADL, ³⁴ walking patterns, ⁴⁶ travel mode ³⁰
Clinical event or disease incidence	5 (16)	1 (3)	6 (19)	Fall, ³⁷ seizure, ⁴² pain, ⁴⁴ freezing of gait ⁴⁵
Disease progression or symptoms	4 (13)	0 (0)	4 (13)	Amplitude and constancy of tremor, ¹⁸ insomnia symptoms, ²⁸ mental disorder symptoms, ³⁶ severity of lung disease ⁴⁸
Treatment patterns	3 (9)	0 (0)	3 (9)	Medication intake, ²⁰ counts of pill medication ²²
Treatment outcomes	0 (0)	3 (9)	3 (9)	Postoperative complications, ^{23,29} patient-reported outcomes following joint replacement ²⁷
Healthcare resource utilization	0 (0)	1 (3)	1 (3)	Hospital admission due to heart failure ³¹
Total	25 (78)	7 (22)	32 (100)	

Note: Values are presented as number (%).
ADL indicates activity of daily living.

Source: Table 2 in Part 1. Please see original paper for references.

RESEARCH ROUNDUP

Section Editor: **Aakash Bipin Gandhi, BPharm, PhD**, Research Scientist, RWE, Sanofi, Cambridge, MA, USA

Availability, affordability, access, and pricing of anti-cancer medicines in low-and middle-income countries: a systematic review of literature.

Ocran Mattila P, Ahmad R, Hasan SS, Babar ZUD. *Front Public Health*. 2021;9:628744. doi: 10.3389/fpubh.2021.628744.

Summary

The present systematic review study focused on assessing the pricing, availability, affordability, and access of anticancer medications in low- and middle-income countries. The review included 13 studies that focused on information related to pricing, availability, affordability, and access parameters.

Relevance

The present study found that existing pricing policies or lack of the same are associated with varying cancer medication prices within and across countries. Further, lesser affordability was consistently observed within low-income populations. The study also found that the major barriers to cancer medication use and access were cost, restricted coverage through public insurance programs, exclusion from essential medicines list, and nonavailability. Dearth in information regarding pricing and affordability data of cancer medication can impact the development of transparent policies to improve access. Hence, initiatives that focus on collecting highly reliable data on these factors is required for developing patient-centered pricing models to improve cancer medication affordability. Further, buying capacity of national governments coupled with joint stakeholder policies and programs are essential to maintain access to cancer medications for the general population.

Government pharmaceutical pricing strategies in the Asia-Pacific region: an overview.

Verghese NR, Barrenetxea J, Bhargava Y, Agrawal S, Finkelstein EA. *J Mark Access Health Policy*. 2019;7(1):1601060. doi: 10.1080/20016689.2019.1601060.

Summary

The present review discusses formal pricing strategies that are being adopted by governments in the Asia Pacific (APAC) region to counter increasing costs of pharmaceutical medications. The study identified (1) internal reference pricing (IRP), (2) external reference pricing, (3) special pricing agreements, (4) pharmacoeconomic evaluation, (5) cost-plus pricing, (6) price maintenance premium, and (7) tendering/negotiations as the 7 most adopted pricing strategies by APAC countries to contain prescription medication costs. Each pricing strategy may have its own merits or is associated with certain concerns. For example, internal reference pricing strategies can introduce price competition in the market by limiting variation in drug prices within a therapeutic class, thus consequently pushing down prices to the least expensive medication (usually a generic).

Further, strategies such as cost-plus pricing that place an explicit limit on what price can be set for a medication help protect vulnerable patient populations (eg, patients with rare diseases) from drug manufacturing monopolies-driven high pricing. The biggest concern associated with pricing strategies is the lack of transparency, especially on rebates and discounts.

Relevance

Pricing strategies are essential for containing high medication costs, fostering price stability, encouraging innovation, and improving short- and long-term drug access.

Access to cardiovascular disease and hypertension medicines in developing countries: an analysis of essential medicine lists, price, availability, and affordability.

Husain MJ, Datta BK, Kostova D, et al. *J Am Heart Assoc*. 2020;9(9):e015302. doi: 10.1161/JAHA.119.015302. Erratum in: *J Am Heart Assoc*. 2020;9(10):e014543.

Summary

The present study reported results for a cross-country evaluation of the availability, pricing, and affordability of cardiovascular medications with an aim of identifying pathways to improve access to treatment. The authors checked for the inclusion of 12 key cardiovascular medications across the essential medications list for 53 countries. Information on the availability, pricing, and affordability of these medications was obtained through surveys conducted across countries based on the World Health Organization's Health Action International survey methodology. On average, 54% and 60% of the medications included in the study were found to be available in low- and middle-income countries (LMICs) and high- and upper-middle-income countries, respectively. Further, on average, availability of medications was higher for generic (61%) as compared to brand (41%) medications. In terms of pricing, the average patient median-price ratio was higher for brand (80.3) compared to generic (16.7) medications. This difference was more pronounced in LMICs across all included medication categories. Affordability was also found to be the lowest in LMICs.

Relevance

For improvement in long-term cardiovascular outcomes, it is essential to have consistent access to appropriate medication. Low availability and high costs continue to remain barriers to adherence for these medications worldwide.

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

Making an Impact: ISPOR Outstanding Chapter Award 2022

An Interview With the ISPOR 2022 Outstanding Chapter Award Winners: Shanghai, Slovakia, and Argentina Chapters

The ISPOR Outstanding Chapter Award program recognizes ISPOR regional chapters' outstanding contribution and leadership in advancing ISPOR's mission in global regions: Asia Pacific, Latin America, and Europe, Middle East, and Africa. The ISPOR Shanghai, Slovakia, and Argentina chapters have been recognized for their exemplary achievements in advancing health economics and outcomes research (HEOR) in their regions. This award is based on a thorough review of chapters' impact on HEOR and health policy in their regions through activities, including education, research and engagement, and contribution to ISPOR strategic initiatives, as described in their annual reports.



LARGE-SIZED CHAPTER

Wen Chen, PhD

President, ISPOR Shanghai Chapter
Fudan University, China

What is something that you are really proud of your chapter for and why? What lessons can other chapters learn from the ISPOR Shanghai chapter?

One of the most important attributes of the Shanghai chapter is that we work closely with policy development and implementation, therefore, our work can directly contribute to supporting decision making. Members in the Shanghai chapter have actively participated in pharmacoeconomic/health technology assessment (PE/HTA) appraisal for the national health insurance negotiation with manufacturers and served on the PE Expert Panel to provide technical support for the update of the National Reimbursement Drug List. Given this intrinsic feature, I am proud that the Shanghai chapter has provided a platform for both scholars and policy makers to communicate and exchange opinions.

As a regional chapter, it is important to create an environment to encourage active engagement in both scientific research and the policy-making process—from value dissemination to daily communication.

How would the chapter use being the recipient of this award to improve healthcare decision making in China?

This award is an outstanding recognition of the efforts made by our team and chapter members and has been very motivating for me and the Shanghai chapter. Although we are still facing enormous challenges during the pandemic, the chapter will continue to facilitate a growing awareness of HTA in China and commit to evolving scientific activities and policy-related activities, participating in relevant conferences and virtual meetings, and organizing more educational training sessions.

According to the chapter, what HEOR trends do you think are the most relevant and most important to focus on? How do you see the future of HEOR evolving in your region?

HEOR is booming in China. We now have the China Guidelines for Pharmacoeconomic Evaluations published and the process of PE/HTA appraisals during national health insurance negotiation. With the flourishing growing trend in China, we expect and call for more practical and operational instructions being released to guide the HTA practice in China.

As HEOR is becoming more commonly used in the field of healthcare and related decision making, a strong talent team with expertise in HEOR will be needed and there will be more HEOR work that needs to be conducted locally. We are positive about the future of HEOR and will focus more on talent building through educational activities and communications between scholars and policy makers.



MEDIUM-SIZED CHAPTER

Lucia Hlavinkova, PhD

President, ISPOR Chapter Slovakia
NovoNordisk, Slovakia

Tell us what this award means for the Chapter and your country?

We see this award as a great recognition that we are doing the right things at the right time and in the right place. It is very motivational for us and gives us the energy and enthusiasm to continue our endeavors to further improve the level of the pharmacoeconomics in Slovakia.

The ISPOR Chapter Slovakia was originally established as a strong expert community 15 years ago. The chapter has entered its era as an institutionalized organization with solid scientific foundation since 2014 under leadership of Mária Bucek Pšenková, MPH, MSc (HTA), currently past-president of the chapter. This award is an appreciation of the long-term efforts of ISPOR Slovakia and obliges us to continue to support and further improve decision making in healthcare in Slovakia.

According to the chapter, what HEOR trends do you think are the most relevant and what's important to focus on? How do you see the future of HEOR evolving in your region?

In our region, we most often encounter healthcare systems that are financially undersized. For this reason, in order not to perceive innovation as only a cost driver, it is necessary to prove and quantify benefits of innovation and talk about it. While costs might only appear as a simple expression of the amount of money per unit, they should in fact be seen as incremental costs over existing costs spent. At the same time, these costs range from direct medical costs, through socioeconomic costs, to social costs. On the benefits side, its measurement and quantification are even more complex. It is therefore necessary that methodologies and approaches to measure costs as benefits in healthcare continue to be developed and implemented in regional and national decision-making processes. We want to maintain our efforts in building high-quality, evidence-based HTA standards, as this allows payers to make good, informed, and sustainable decisions for patients and society as a whole.

What contributions have the chapter made in HEOR and healthcare decision making that are most meaningful to you?

In February 2022, the ISPOR Chapter Slovakia published the second edition of local pharmacoeconomics guidelines, which was created as an update of the guidelines issued in December 2020. Historically, the first edition of the Slovak pharmacoeconomic guidelines of professional societies was developed as a response to a broad demand for methodological recommendations that would consider current international trends in the pharmacoeconomics, as well as guidelines of international professional societies. The first edition received a positive response from the professional community. Pharmacoeconomics is a dynamic and rapidly evolving scientific discipline. After just over a year, our chapter helped develop the second edition of the guidelines, which has been supplemented

by new knowledge and sources of information, including ISPOR's updated Consolidated Health Economic Evaluation Reporting Standards, CHEERS 2022. Most importantly, decision makers are now aware that approaches to health economic evaluation need to be updated and the latest knowledge incorporated into real-world practice.



SMALL-SIZED CHAPTER

Olga Andrea Alcaraz, MSc, PhD, MD

President, ISPOR Argentina Chapter
Instituto de Efectividad Clínica y Sanitaria, Argentina

According to the chapter, what HEOR trends do you think are the most relevant, and what's important to focus on? How do you see the future of HEOR evolving in your region?

The use of real-world evidence is projected as one of the growing interests in the region. It is crucial that progress on this topic be made with the highest quality possible and join efforts to establish reliable sources of information. It will also be necessary to discuss the feasibility of using the data generated in decision making to incorporate new technologies.

On the other hand, the high cost of new technologies continues to be a critical problem in the region. Establishing clear rules regarding cost-effectiveness and budget impact thresholds is essential to have clear rules. This could favor improving the judicialization of health—a very important topic in the region.

What contributions have the chapter made in HEOR and healthcare decision making that are most meaningful to you?

The chapter tries to position itself as a space for dialogue between the different decision-making stakeholders for the incorporation of health technologies in Argentina. During the past year, we worked on the issue of joint venture agreements, where this interaction is critical for the success of the chapter. A [webinar](#) was held to raise awareness about collaboration possibilities and a survey was sent to understand the barriers and facilitators for its implementation. A workshop is planned to establish priorities for action.

Going forward, do you have any goals as an ISPOR chapter president? What has been your biggest challenges and lessons learned from this role?

The greatest personal challenge is to facilitate the dialogue of all the actors in the health system who sometimes have time limitations or certain resistance to the discussion. Coming from an academic background, I try to leave that imprint on my activity in the chapter. We are lucky to have a very interdisciplinary chapter, where we have different professions and fields of work, which significantly enriches the discussions and projects. Being that this is a small chapter, maintaining active participation with a stable position in the country is my main objective as a chapter president.

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Research & Case Study	January 12	Week of February 27

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- Explore the healthcare systems pathways through which medical devices can be implemented.

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- Learn how to design survey instruments and data collection strategies to reduce the risk of fraudulent responses.
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TRANSPARENT DRUG PRICES MAY NOT HELP IN EXPANDING ACCESS

By Christiane Truelove



When it comes to creating more equitable access for new and innovating medicines, experts generally agree that it would be more useful to establish a pharmaceutical's true value in different settings, rather than exposing its price. Revealing actual prices that the pharma industry gives to payers in low- and middle-income countries (LMICs) would simply encourage the exportation and resale of those products to higher-income countries. Additionally, establishing price transparency as a global concept would just make a price convergence where LMICs are forced to pay a higher price than they would have under the current tendered agreement system. Health economics and outcomes research (HEOR) experts working on increasing equity in new medicines (whether those already in the field or still in school), will need to understand the economics behind pricing to make effective value arguments to those in pharma setting these prices.

The conundrum of transparency

The World Health Organization continues to push for net pricing transparency to help increase pharmaceutical equity and access (https://apps.who.int/gb/ebwha/pdf_files/WHA72/A72_R8-en.pdf). Meanwhile, in the United States, some policy makers have proposed external reference pricing (ERP), which would tie prices for high-cost drugs to those in other countries. For European Union members, the question remains whether it's possible to achieve pricing transparency of new medicines and have it control costs and increase access for LMICs.

"There is certainly a lot of buzz internationally and there are working groups that focus on price transparency," says Daniel Ollendorf, PhD, MPH, Director of Value Measurement & Global Health Initiatives, Center for the Evaluation of Value and Risk in Health and Assistant Professor, Tufts University School of Medicine. "I think the challenge is—and we don't actually only see this play out in the United States because, increasingly in international settings, a new product is only adopted after confidential discounts are negotiated—that international reference pricing is becoming more fictional over time, given that it's not actually the price that's paid in any given jurisdiction that's being reflected."

HEOR experts working on increasing equity in new medicines will need to understand the economics behind pricing to make effective value arguments to those in pharma setting these prices.

Compounding this is the pharma industry's belief that the ability to charge different prices for the same product, depending on the setting, is a key feature of the success of the pharmaceutical ecosystem, Ollendorf says. "And to a certain extent, I agree with that. But it's compounded when you're dealing with a situation like we have in the United States and in other countries as well, where it's not just major payers or

insurance schemes that are negotiating different prices—it's a different price for not only the payers (eg, commercial payers in the United States) but even for the different benefit plans that those individual payers provide. So, it becomes a much bigger game of cat and mouse, so to speak. And then there is an increasing incentive to be less and less transparent about it, if you know that you're trying to shield whatever you pay from your competitor."

Graham Cookson, PhD, MSc, Chief Executive of the Office of Health Economics in the United Kingdom, says he looks at the pricing transparency issue from his standpoint as an economist. "It feels a bit contradictory because most of us would say transparency must be a good thing, right? If you're not transparent, you must be hiding something and that there's something nefarious going on if you're not willing to be completely transparent about something," Cookson says. "There's this ideal that we hold that transparency is good in itself."

The problem is that "nontransparency, confidentiality, or opaqueness is actually fundamental to ensuring that pricing in pharmaceuticals works effectively," Cookson says. "It's fundamental to maximizing social value and maximizing access."

"The problem is that nontransparency, confidentiality, or opaqueness is actually fundamental to ensuring that pricing in pharmaceuticals works effectively."

— Graham Cookson, PhD, MSc

Jens Grueger, PhD, Partner and Director, Market Access and Pricing in Health Care at Boston Consulting Group, noted that when it comes to price transparency, there are 2 very different areas to look at: (1) the confidential tendering and commercial contracting process in determining prices, and (2) the use of reference pricing.

"The first one is about tendering and competitive contracting of therapies in the same class, or even the same molecule that comes from different sources—and I haven't heard that anybody is concerned about the confidential nature of these tenders. There is a very clear, transparent process," Grueger says, "and there is a feeling that if we do the commercial tendering or contracting, that we can get better prices for that. There is some literature that also suggests that if we were not doing it confidentially, we would not be getting such good outcomes, because if I know what my competitor has bet the last time, I would somehow coalesce around that price point. I wouldn't be as aggressive if I have lost the first tender; I would probably go deeper in my prices."

Where the question of transparency comes up most frequently, however, is when there is contracting for new

medicines or more expensive patent-protected medicines. “There we have to ask the question, ‘Why did we get to these confidential agreements?’ Many of these agreements started in Europe, because in Europe, there is international trade, parallel trade, which is allowed because all of these drugs are approved on the same license through the European Medicines Agency,” Grueger says. “You can trade them between different countries and there is price referencing where countries are looking at each other.”

Grueger and Cookson note that this European reference pricing works well when the countries are similar in wealth, but not so well when comparing wealthier countries with LMICs.

“Price referencing makes sense when you have countries that have similar economic situations,” Grueger says. “But even within Europe, when you compare Germany or Denmark or Belgium with Romania and Bulgaria, there is a 3-fold difference in gross domestic product per capita.”

But in looking at LMICs, Cookson says the price transparency debate misses what the fundamental problem is. “If you look at pharmaceutical expenditure in LMICs, something like 90% to 95% of pharmaceutical expenditure is on off-patent medicines. So, this conversation about price transparency is completely irrelevant because the conversation generally about price transparency is about new medicines, branded medicines, on patent medicines.”

“Price referencing makes sense when you have countries that have similar economic situations. But even within Europe, when you compare Germany or Denmark or Belgium with Romania and Bulgaria, there is a 3-fold difference in gross domestic product per capita.”

— Jens Grueger, PhD

Because the majority of drug spending in LMICs is on generic medicines, the question to ask is why the prices of generics are relatively high. “I think there’s a lot of costs being added. Freight, the logistical elements of delivering these products to these markets, and getting them out there” can drive up prices, Cookson says. Additionally, much of the costs for patients relate to out-of-pocket expenses, which isn’t really related to the price of the pharmaceuticals, but the lack of universal health coverage in those markets.

Adding to the murkiness is “it’s really, really difficult statistically to do any work that tries to look at the real prices that are being paid in different markets,” Cookson says. “Because you really need to understand supply chain factors, exchange rate costs, and cost of capital, transportation costs in each of these markets to see where there is a fair or unfair variation in price.

And I think some of the studies that have been done are quite simplistic and failed to look at some of these legitimate reasons why prices may fluctuate across different markets in different locations and of different sizes.”

“If you look at pharmaceutical expenditure in LMICs, something like 90% to 95% of pharmaceutical expenditure is on off-patent medicines. So, this conversation about price transparency is completely irrelevant because the conversation generally about price transparency is about new medicines.”

— Graham Cookson, PhD, MSc

When it comes to pricing, Ollendorf says it should be based on value. “I am a proponent of value-based pricing. Pricing that’s aligned with value should be used to set ceiling prices. Then, anything beyond that (ie, whether an individual payer is able to negotiate), kudos to them. But that way, we can at least be transparent about the starting point.

“To a certain extent, that still is the way that reference pricing operates. The problem is that because all the countries in Europe reference each other, essentially, everything is getting inflated.”

Grueger notes that many of the European countries that have been pushing for net price transparency are wealthier ones, including Italy and Norway. “Why are they interested in that transparency? Well, I think they want to benefit from lower prices in countries that have a lower income level and deserve to get lower prices,” he says. “I haven’t heard that Serbia or Croatia in Europe, or that Egypt or Morocco in Africa have been pushing for price transparency. I think these countries are quite happy that they can get the lower prices at this point in time. If this facility of a net price arrangement didn’t exist, they wouldn’t get the product anymore into their countries.”

When it comes to countries negotiating together for a uniform price on innovative but expensive new medicines, the pharma industry is not concerned with constructs such as Beneluxia (ie, Belgium, Netherlands, Luxembourg, Ireland, and Austria), which are all countries that are similar in economic ability, according to Grueger. “They just simplify the process: they do 1 negotiation instead of 5; they increase the negotiation power, but also the ability to do proper assessments of these products,” he says.

Where the industry does get concerned, however, is if Italy would try to negotiate together with Romania, or Romania with Turkey and Kenya. “These are very different situations and that’s the thing the industry is very concerned about,” Grueger

says. “The problem is just that everything converges to the lowest price in the basket.”

With these lowball offers, the pharma industry believes it is not getting rewarded for innovation and will be reluctant to accept these prices. “That means everything might converge towards the higher end, and then the countries that cannot afford these prices will not be able to purchase, which is also bad for the industry,” Grueger says. “Industry wants to open up the market. Nobody in the industry says we are only developing products for North America and Western Europe. There is a strong commitment to also make these products available in countries that have a high unmet need and have a low ability to pay.”

Value-Based Pricing and the Future of HEOR

Students of HEOR—whether they are thinking about working for pharma, payers, or health technology assessment (HTA) agencies—need to understand how pricing works in the industry, as well as the economic system drivers of pricing, so they can create new mechanisms for value-based pricing, experts say.

“Given that these are trained [HEOR] professionals who actually have the tools to inform such a decision, but their input is not routinely taken—that seems to be an incredible missed opportunity.”

— Daniel Ollendorf, PhD, MPH

“Those who are in school and are studying all aspects of the pharmaceutical innovation and pricing ecosystem and may be thinking about jobs in industry, should take a course (or maybe more than 1 course) on how pricing works in the industry,” Ollendorf says. “What does strategic pricing look like? Who does it? How much input did they take from other sectors of the industry, including HEOR? Is there an opportunity to strengthen that conversation?”

According to Ollendorf, he has not seen much action from the industry to integrate HEOR professionals’ opinions into pricing, “given that these are trained professionals who actually have the tools to inform such a decision, but their input is not routinely taken. And that seems to be an incredible missed opportunity.”

However, he has seen some evolution in the thinking about the use of HEOR in creating value pricing. “There’s a venture capital group in Europe that has created a separate fund to invest in small companies that are essentially committing to value-based pricing. So, they’re using those calculations in the very beginning. Another group in Canada is piloting the notion of early HTA to try to understand what the clinical and financial headroom for a new product is within the confines of how an HTA body or a major payer might make a decision about it.

“So, there is some understanding about the value delivered for the price that’s commanded. But there has to be much more of that. I would urge students to find out as much as they can about how pricing happens now. What are the issues with it? What might be done to improve the picture moving forward?”

Cookson says having a solid understanding of what value-based pricing actually means from an economic perspective is important. “It helps you to start understanding more about how we deal with some of the real challenging problems we’re currently facing. For instance, how do we deal with combination therapies? How do we deal with potentially curative therapies? How do we deal with products where there’s significant uncertainty? And how do we share the risk? Value-based pricing in itself feels like a relatively simple concept. But actually, there’s a lot underneath it that people can study, understand, and apply.”









Presently, there continue to be innovations in value-based pricing and differential pricing. As an example, Cookson says to look at what Europe is doing with equity-based tier pricing, where countries are split into 2 tiers—one slightly richer, and the other slightly poorer. “I think that is going to be really interesting,” he says. “And it’s going to require evidence on how we define the threshold between tiers, and how to then set prices fairly for those 2 or more groups.”

By the Numbers: Global Price Transparency

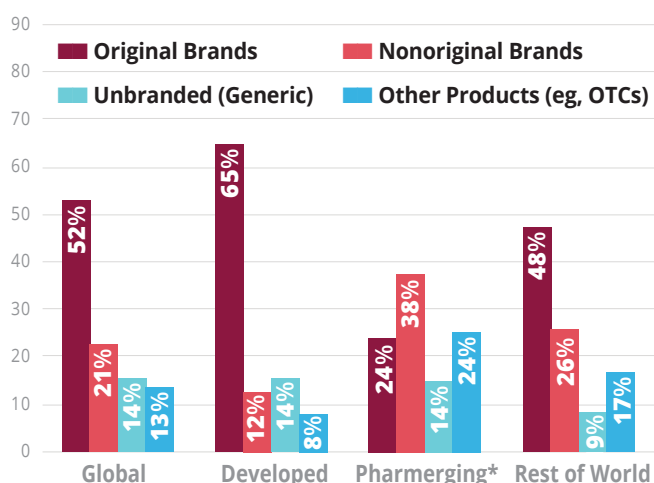
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8 Recommendations for the Use of International Reference Pricing as a National Pricing Policy

International Reference Pricing Aspect	Recommendation
 Scope of international reference pricing	Reimbursement of single-source products
 Composition of country basket	Select 5 to 7 countries with similar socioeconomic and healthcare environments
 Contingency	Stay flexible to adjust for contingencies or temporary distortions
 Definition of price	Exfactory prices free of markups, taxes, and discounts or rebates should be used
 Source of price information	Combine national and international sources and company-certified information
 Price calculation	Calculate the average or median price of the same product in the basket
 Exchange rate	Prevent volatility by applying the average of exchange rates Consider using purchasing power parity exchange rates
 Frequency of price revisions	Allow reasonable time for implementation (not more than yearly or biannually)

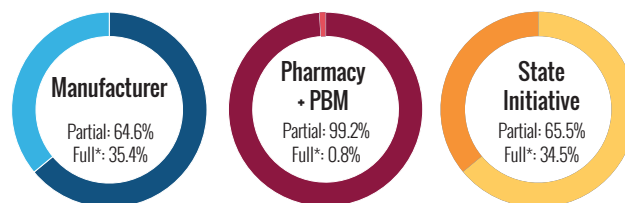
Price transparency and its role in the availability of medicines in LMICs



LMICs indicates lower- and middle-income countries; OTCs, over-the-counter.
*Countries having low position on the pharmaceutical market, but a speed pace of growth (eg, China, India, Brazil, Russia, etc).

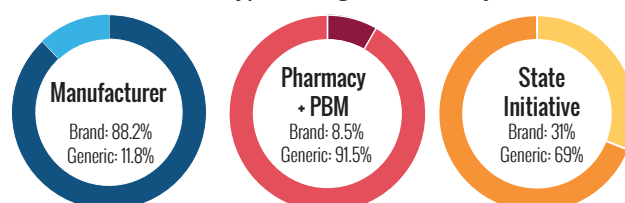
Characteristics of discounts/offsets in the United States by source

Differences in discount type by discount source



*\$0 out-of-pocket costs.

Differences in type of drug discounted by source



PBM indicates pharmacy benefit manager.

Equitable Access to COVID-19 Vaccines in the United States: An Overview of the Evidence-Based Recommendations and Evaluation of the Outcomes

Yejin Lydia Lee, PharmD, Kelly Zhou, BS, Rutgers Ernest Mario School of Pharmacy, Piscataway, NJ, USA; Kelsey Lee, PharmD, Bayer Pharmaceuticals, Whippany, NJ, USA; Hyebina Park, PharmD, Merck & Co, Kenilworth, NJ, USA; Mark Neese, PharmD, MS, Bayer Pharmaceuticals, Whippany, NJ, USA; Zeba M. Khan, RPh, PhD, Rutgers Ernest Mario School of Pharmacy and Center for Health Outcomes, Policy & Economics, Piscataway, NJ, USA

This article focuses on COVID-19 vaccine equity-related issues and recommendations to improve vaccine accessibility in the United States.

US policy and implementation are reviewed and evaluated to impact future outbreak preparedness and equitable access.

Various evidence-based, individual community-based practices are encouraged to improve COVID-19 vaccine health equity.

Introduction

Despite demonstrated positive risk-benefit ratio of COVID-19 vaccines and availability at an unprecedented speed, vaccination rates vary in the United States. Areas with low vaccination rates may increase the risk of severe infections and viral mutations that threaten our progress in preventing the spread of COVID-19. This uneven vaccine distribution has been partly due to health inequity.^{1,2}

Health inequity consists of systematic differences in marginalized, disadvantaged populations with vulnerabilities in various social determinants of health (SDOH). SDOH are defined as the environmental conditions in the places people inhabit, which impact a wide range of health risks and outcomes. Due to SDOH that exacerbate comorbidities, minority populations have a 5 times greater risk of adverse COVID-19 consequences. Thus, equitable COVID-19 vaccine access has been proposed to mitigate the disproportionate effect of the COVID-19 pandemic in underserved populations often predisposed to health inequity.²

Equitable access is more than equal access. Health equity allows all individuals to have the chance to achieve optimal health according to their individual needs. During the COVID-19 pandemic, it has become clear that to achieve health equity in vaccination rates, individualized accessibility solutions addressing SDOH are essential. However, there is only a limited amount of clear, evidence-based, and validated guidance on improving health equity. The objective of this paper is to foster future pandemic preparedness and prevent further delays in health equity by reviewing the recommendation and efforts toward vaccine equity evident during the COVID-19 pandemic.

To achieve this, some of the evidence-based recommendations for vaccine

equity, policy, and implementation strategy will be reviewed. Then the outcomes of the implementation strategy will be evaluated using the equity checklist for Health Technology Assessment (ECHTA) adapted for qualitative analysis.^{2,3}

Recommendations for Vaccine Equity in Policy and Implementation

Public health policy and implementation should utilize multifaceted, evidence-based approaches. Figure 1 lists some high-level recommendations that serve as a nonalgorithmic checklist to encourage a nonbiased, individualized, and collaborative approach to prevent any inadvertent exacerbation of health inequity.

Minority populations have a 5 times greater risk of adverse COVID-19 consequences.

First and foremost, vaccinations should be easily accessible for all, including those with mobility, transportation, geographic, or employment barriers. This may entail vans delivering vaccines, vaccination sites near public transportation hubs, employer-affiliated delivery programs, and operations beyond standard business hours. Employers should implement policies such as paid time off and flexible leave for vaccinations.^{1,2}

As access is established, community partnerships are integral to health equity developments. Inclusion of nontraditional community members such as individuals most affected or familiar with the community would challenge and broaden the perspectives of the decision makers. One of these participations may include involvement in healthcare provider training to help understand the community's vulnerabilities, identities, experiences, and underlying barriers. Community organizations may also serve as vaccination sites, especially in areas

with high vulnerability index scores and morbidity. Consequently, these collaborations lead to trust-building opportunities for the communities to understand the humanitarian motivations of the decision makers.^{1,2}

In order to fortify such trusted relationships, the community should be involved in the development and dissemination of relevant health education to gain public support and overcome vaccine hesitancy. Such campaigns should be culturally sensitive and multilingual while considering individual community-based value elements, lived experiences, political stances, scientific understanding, and perceived motives of healthcare industries. Transparency in health education should be further amplified through investigating adverse reactions and incidental outcomes within and outside the United States.^{1,2}

Likewise, these efforts may benefit from appropriately utilizing technological advancements. This may be achieved through multilingual hotlines, mobile

applications for addressing vaccine-related concerns and scheduling, and simplified registration via phone and in person. Furthermore, real-world evidence may reduce vaccine hesitancy by tracking and reporting the safety and effectiveness of the vaccines.

This insight could be maximized using artificial intelligence for analysis. For these analyses, increased interoperability and coordination among local, state, and national health departments would optimize vaccination capacity and streamline disaggregated comparisons of uptake by race, ethnicity, and geographic location.^{1,2,4,5}

In addition to technological involvement, findings from behavioral and implementation sciences should be utilized to craft and direct the implementations. Different motivations such as moral obligations to not cause harm to others, trusted sources addressing concerns, social acceptability, autonomy, or societal liberty should be addressed.^{1,2} According to a recent study, behaviors indicative of reducing the spread of the virus, perceived increased

risk of infection, and a high degree of communicability were positively associated with COVID-19 vaccine willingness and acceptance.⁶

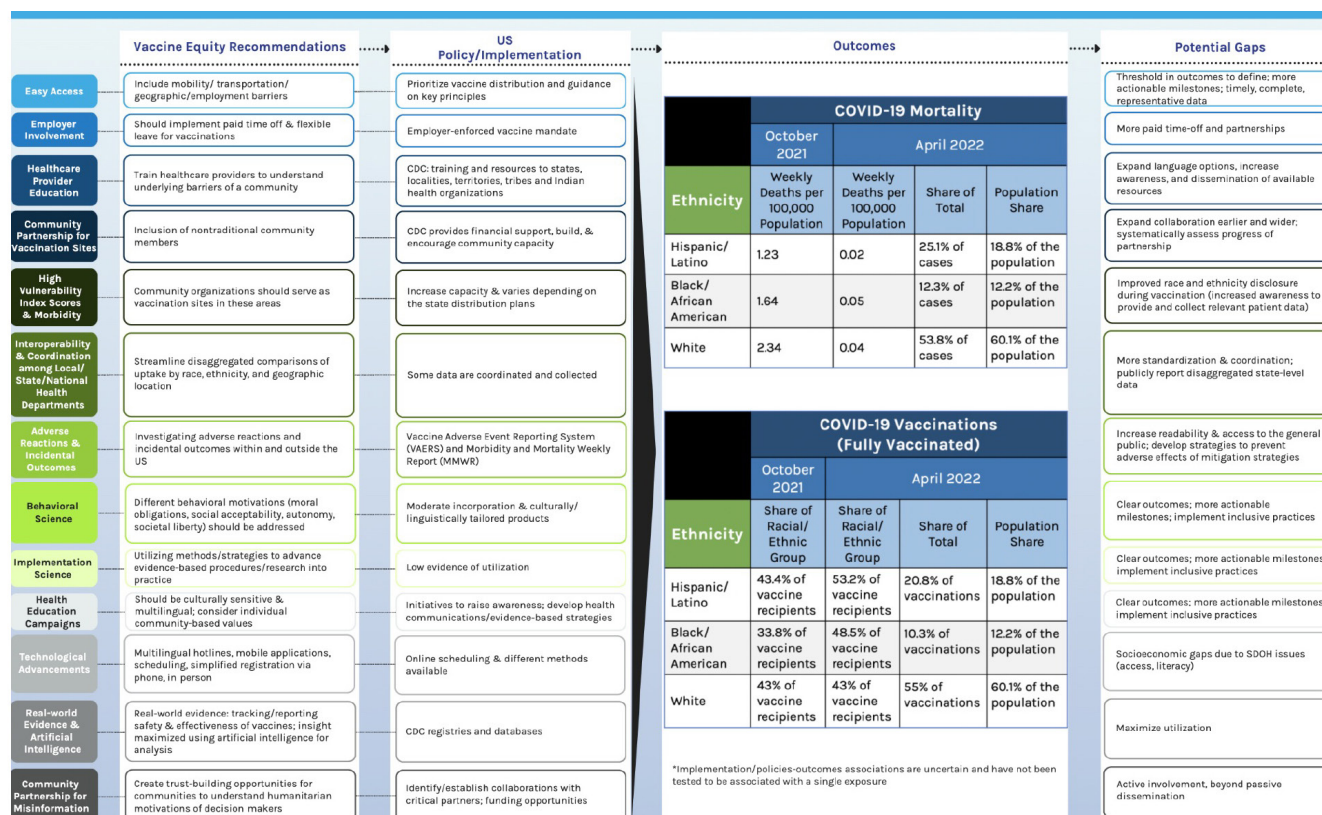
Overview of Policy and Implementation

These recommendations demonstrate ways to improve health equity within policy and implementation. Some key US policy and implementation strategies addressing health inequity are outlined with recent outcomes related to COVID-19 and existing gaps in **Figure 1**.

Evaluation of Policy and Implementation

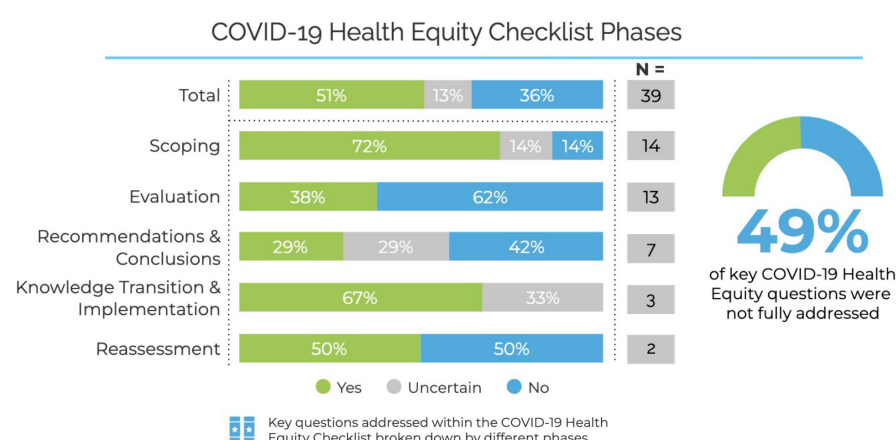
Despite ongoing efforts, there are gaps to be addressed for equitable COVID-19 vaccine access in the United States. Evaluation of US policy and implementation strategies revealed that 49% of health equity questions were not adequately addressed (**Figure 2**). This may imply insufficient publication of the efforts or inadequate health equity strategy. The scoping, knowledge transition, and implementation phases seem to be well addressed while the

Figure 1. Vaccine equity recommendations, US policy/implementation, and potential gaps*¹⁻⁷



CDC indicates Centers for Disease Control and Prevention; SDOH, social determinants of health; US, United States.

Figure 2. Equity checklist for health technology assessment adapted for evaluating COVID-19 health equity^{2,3} (Adapted from Benkhalti, et al)³



The breakdown of the checklist phases is available upon request.

evaluation, recommendations, and conclusion phases had the most uncertainties.

To highlight some uncertainties, a better data strategy, a threshold in outcomes to define and measure improvement, and more actionable milestones are essential. In fact, of the total vaccinations data collected by the Centers for Disease Control and Prevention (CDC), approximately one quarter has unknown race and ethnicity. Hence, race and ethnicity disclosure should be encouraged through provider and patient education.

Asian (59%) and White (54%) received the highest shares of booster doses, while less than half of Black (44%) and Hispanic (40%) received booster doses.

These vaccine-related data should also be standardized and coordinated across all stakeholder groups while incorporating best practices regarding real-world evidence and artificial intelligence. Consequently, these data—coupled with patient engagement—may uncover clear outcome measures and thresholds focused on patient perspectives beyond aggregated vaccination rates. Last but not least,

unclear timelines and goals may hinder accurate assessment of the strategies even with optimal data strategy. Future health equity strategies should account for all of these critical gaps (Figure 1).

Outcomes

Equitable access to COVID-19 vaccines has been improving in the United States with ongoing policies and implementations (Figure 1). As of March 9, 2022, the CDC showed that 76.5% of the total US population received at least 1 dose and 65.5% of the total US population were fully vaccinated.⁵ Although initially, Black and Hispanic/Latino have been less likely than their White counterparts to receive the COVID-19 vaccine, these disparities have decreased over time and even reversed for the Hispanic/Latino population.⁴ Such a gradual increase in vaccination rates may reflect the incremental success of the policy and implementation. Other external factors such as emergent variants and increased vaccinations among the younger population may have also contributed to this improvement.⁴

However, with booster doses, delay in the minority population persists—Asian (59%) and White (54%) received the highest shares of booster doses, while less than half of Black (44%) and Hispanic (40%) received booster doses, which purports that achieving equitable access is an ongoing process, requiring sustainable strategies and measurements.⁷

Closing Remarks

Adaptation of these recommendations and evaluations—coupled with the most up-to-date literature, government resources, and policies—should serve as an initial guide to impact future outbreak preparedness and equitable access. This suggestion is partly due to some of the limitations of the paper. First, similar to other literature on health equity, this paper only provides high-level, nonspecific qualitative assessments. The main reason for this is the individualization necessary when addressing SDOH decisions specific to a community. Furthermore, the ECHTA has been made to evaluate health equity in health technology assessment processes, not necessarily policy or implementation considerations. Thus, more systematic research is needed to develop tangible, quantitative recommendations and evaluations to ascertain equitable access to vaccinations during future outbreaks and emergencies.

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Socioeconomic Influences on County-Level Differences in COVID-19 Incidence During the Second Wave in Germany

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This study investigated a correlation between COVID-19 incidence rates and socioeconomic parameters among 401 German counties.

In the second wave of infections, more individual space was crucial for low regional incidence rates.

Introduction

In the fall of 2020, Germany entered a severe second wave of COVID-19, recording 4 to 5 times more cases and fatalities per day than during the first wave of the pandemic, with 2,028,851 cases and 55,642 COVID-19-related fatalities between October 5, 2020 and February 12, 2021.¹ The second wave can be divided into 3 distinct phases of rising, stagnant, and falling infection rates (**Figure 1**).

Phase I (October 5 to November 5, 2020) corresponded to a rapid rise in daily new cases (**Figure 1**), following a peak vacation period during federal school holidays in all counties in Germany.² Only limited COVID-19-related governmental restrictions were in place during most of phase I.³

Phase II (November 6 to December 6, 2020) showed a steady high level of transmissions (**Figure 1**). Starting on November 2, 2020, the German government imposed a partial lockdown, closing the hospitality and culture sector and limiting social contacts to 2 households. Schools and businesses remained open.³

The period from December 7, 2020 to January 1, 2021 was excluded from our analysis due to high fluctuations in incidence rates. Another rapid increase in cases during the first half of December led to the declaration of a full national lockdown commencing December 16, 2020.³ On December 24th, the first case of the Delta variant was confirmed. Shortly after, the vaccination program began on December 27th, albeit initially limited to caregivers, those aged over 80 years, and other vulnerable persons.

Phase III (January 12 to February 12, 2021) showed a slow but continuous decline in daily new COVID-19 cases (**Figure 1**). On January 14th, one million (1.2%) German inhabitants had received their first dose of a COVID-19 vaccine. The full national lockdown was prolonged until mid-February, with a newly introduced mandate for medical or higher-grade masks in all closed public spaces³ and for home offices. Schools and day care centers were closed.^{2,4}

We analyzed the substantial differences of rising, stagnant, and falling COVID-19 incidence rates across Germany during phases I to III in the context of varying socioeconomic factors. Other studies

Figure 1: Number of new daily COVID-19 cases in Germany between September 1, 2020 and March 1, 2021.

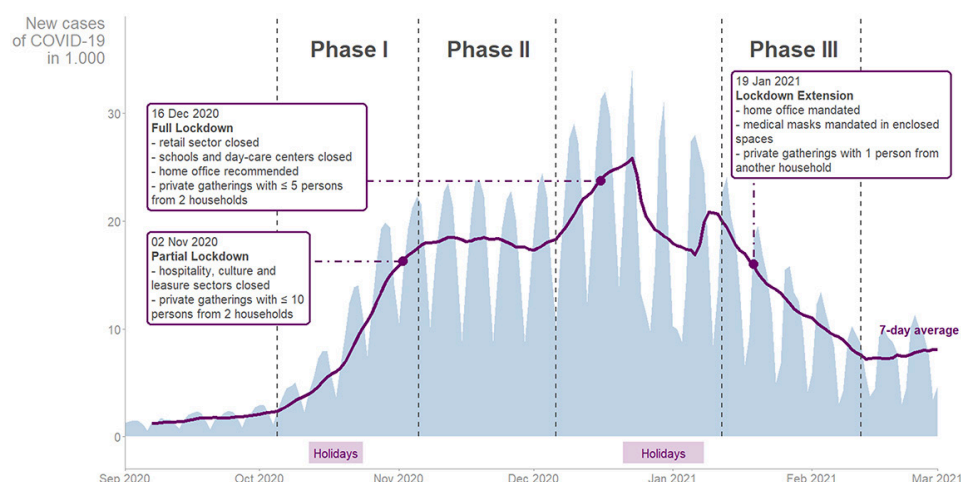


Table 1: Descriptive summary statistics for the included socioeconomic variables and standardized COVID-19 incidence during the 3 phases of interest.

	Median	Mean	SD	Min	Max
Population density (inhabitants/km ²)	200.5	537.0	709.7	35.6	4777.0
Household size (individuals/household)	2.2	2.2	0.2	1.8	2.8
Living space (m ² /inhabitant)	45.2	45.3	3.8	36.9	57.7
Disposable income (€/inhabitant)	23,412.00	23,542.79	2797.52	17,015.00	42,275.00
Abitur (% of inhabitants)	32.5	32.7	8.6	10.5	64.0
cases/100k inhabitants:					
Phase I (October 5–November 5, 2020)	335.43	349.08	172.16	56.73	1074.51
Phase II (November 6–December 6, 2020)	620.32	634.94	289.81	63.63	1756.42
Phase III (January 12–February 12, 2021)	430.70	491.90	226.54	142.98	1440.97

SD indicates standard deviation.

found socioeconomic factors to play a role in the speed and extent of transmissions within a community.^{5–7} There is considerable heterogeneity between German counties in socioeconomic factors, which allowed us to infer likely drivers of COVID-19 transmissions even in the absence of information on individual patients. The current study assumed common underlying socioeconomic factors influencing transmission dynamics for all 401 counties of Germany.

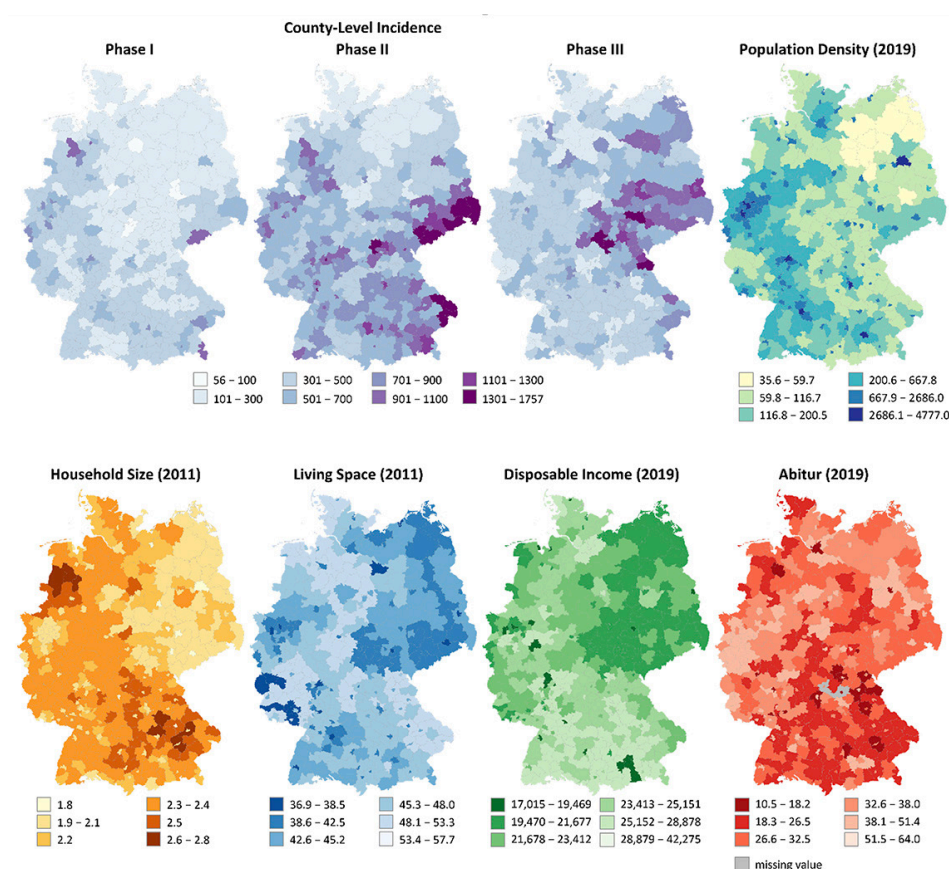
Methods and Results

We investigated whether selected socioeconomic factors could predict COVID-19 incidence at county level.

Variable selection was limited by the availability of current county-level data (see **Table 1** for summary statistics of included variables). Data were retrieved from the open-access statistics portal “Regionalatlas Deutschland.”⁸ Selected variables were population density as inhabitants/km² (henceforth referred to as “PopDens”, data from December 31, 2019), average household size as individuals/household (“HHSIZE”, May 9, 2011), average living space per building as m²/inhabitant (“LivSpace”, May 9, 2011), average disposable income as EUR/inhabitant (“income”, December 31, 2019), and the percentage of inhabitants with a university-entrance degree (“Abitur”, December 31, 2019). The county-level distribution of each variable was plotted to heat maps (**Figure 2**).

COVID-19 incidence rates were retrieved from the Robert Koch Institute’s COVID-19 data hub, based on daily new cases reported by health institutions in

Figure 2: County-level distribution of COVID-19 incidence in phases I, II, and III, and of the 5 included socioeconomic variables.



Germany’s 401 counties.⁹ We extracted data corresponding to the predefined phases I to III and standardized to cases per 100,000 inhabitants by dividing the reported absolute number of a county’s daily new cases by its population size as of December 31, 2019, multiplied by 100,000 (“cases/100k”). Finally, daily new cases/100k were summed per phase and per county and plotted to heat maps (**Figure 2**).

For each phase, we computed a robust linear regression model in R (“lmRob” function of the package “robust”) with PopDens, HHSIZE, LivSpace, income, and Abitur as predictor variables for cases/100k (**Table 2**).

In our analysis, socioeconomic regional differences significantly predicted COVID-19 incidences during the 3 phases. However, in contrast to phases I

Table 2: Robust regression of COVID-19 incidence in phase I, phase II, and phase III.

Phase I	Population density	Household size	Living space	Disposable income	Abitur
beta	0.18	0.42	-0.20	0.18	-0.09
P	<0.001	<0.001	<0.001	<0.001	0.093
$R^2 = 0.44;$	<i>multiple $R^2 = 0.32;$</i>	$F = 44.17;$	$P < 0.001$		
Phase II					
beta	0.13	0.39	-0.22	0.12	-0.15
P	<0.001	<0.001	<0.001	0.002	0.005
$R^2 = 0.32;$	<i>multiple $R^2 = 0.26;$</i>	$F = 31.79;$	$P < 0.001$		
Phase III					
beta	-0.06	-0.14	-0.22	-0.16	-0.11
P	<0.001	0.027	<0.001	<0.001	0.038
$R^2 = 0.18;$	<i>multiple $R^2 = 0.08;$</i>	$F = 8.64;$	$P = 0.110$		

and II, the predictive power of our model for phase III was weak (Table 2).

LivSpace showed the most consistent correlation with COVID-19 incidence for phases I to III. Throughout all 3 phases, counties with less LivSpace showed consistently more cases/100k than counties with more LivSpace.

PopDens, HHSIZE, and income showed a significant positive correlation with cases/100k during phases I and II, but a negative correlation during phase III. During phases I and II, more cases/100k were reported in counties with greater PopDens, greater HHSIZE, and, interestingly, higher income. However, during phase III, this relationship reversed. During phase III, the higher a county's PopDens, HHSIZE, and income, the fewer cases/100k it reported (Table 2).

Abitur was not a reliable predictor of COVID-19 incidence.

Discussion

Social disparities were considered in other studies as one of the leading factors influencing COVID-19 infections, especially in periods of rising incidences.⁷ Workers with frequent face-to-face contact with potentially infected individuals or those in cramped workplaces might be most likely at risk of contracting COVID-19. Particularly affected might be workers in occupations with low academic requirements and low pay, such as those considered essential services (cleaning, public transport, etc) and those relying on temporary work with limited possibility to take leave.⁷ Although our assumption was that, on

an individual level, higher income and education would correspond to greater work flexibility and more compliant behavior and thus a decreased risk of infection, on a county level, we did not see such a connection. Higher income, used as one indicator for social disparities across German counties, was associated with higher COVID-19 incidence when cases were rising or stagnant during phases I and II. The reasons for this are unclear as relevant data on behavior are lacking.

Social disparities, here measured through differences in income and education, seemed to play a subordinate role in determining areas of high incidence during periods with limited governmental intervention.

The percentage of inhabitants with Abitur showed a weaker and inconsistent connection to a county's incidence rates. We conclude that Abitur has a weak connection to risk-relevant behavior or variables such as LivSpace or income. In Germany, inhabitants with Abitur have only a marginally higher amount of average lifetime earnings compared to inhabitants with vocational training.¹⁰

LivSpace, HHSIZE, and PopDens are indicator variables for individual space. The spatial factor in addition to exposure time is a key determinant for COVID-19

infection risk. These space-related variables reflect the general potential of inhabitants within a county to socially isolate and decrease their individual exposure risk. Thus, we expected a consistently strong correlation with incidence rates for these variables during all 3 phases.

While this was true, a strong correlation was observed only for phases I and II. Hence, sufficient individual space was a crucial factor for lower COVID-19 transmissions within a population in times of accelerated increase or steady high level of transmissions and with limited governmental restrictions (phases I/II). Interestingly, our chosen variables lost their predictive value in times of strict lockdown conditions (phase III). Although the correlations modeled for phase III allow no meaningful interpretation, it is intriguing to contemplate potential causes for the correlation loss.

Why did our selected variables lose influence in phase III? The introduction of nonpharmaceutical interventions—particularly the full national lockdown—in phase III likely disrupted the influence that was observed in the previous phases. The closing of schools and a work-from-home mandate reduced contacts outside one's household to a minimum and affected all households. Of our indicator variables for individual space, HHSIZE may have lost impact as multiplier after virus introduction into the household because of the restrictions on interhousehold encounters; PopDens may have lost impact due to reduced contact possibilities under lockdown restrictions

(work-from-home, closed schools, etc). Of all the spatial variables, only LivSpace seems to have maintained a measurable effect.

What driving factors could be influencing incidence in phase III? Instead of county-level factors, COVID-19 incidence in phase III seems rather determined on an individual level. Determinants may have been individual possibilities to reduce nonhousehold contacts and individual levels of compliance. One's occupation and potential to work from home likely had a major influence on infection risk but cannot easily be measured as the occupations classified as essential (and thus exempt from work-from-home mandates) covered a wide range independent of income or other social factors. Individual compliance with lockdown measures is another important contributing factor but cannot be measured through county-level variables. A follow-up investigation of the driving factors in phase III would give more insight into the socioeconomic dynamics in times of declining COVID-19 cases under strict lockdown conditions.

In conclusion, socioeconomic factors played an important role in the ease of transmissions within a population during the second wave of infections of the COVID-19 pandemic in Germany. During periods of exponentially rising or consistently high incidence rates with limited governmental intervention, providing sufficient individual space within an area, here measured by LivSpace, HHSIZE, and PopDens, was crucial in facilitating low daily incidence rates. Social disparities, here measured through differences in income and education, seemed to play a subordinate role in determining areas of high incidence during periods with limited governmental intervention.

Our analyses were limited to a small selection of variables of interest potentially affected by multicollinearity, influencing the interpretations that could be drawn in this occasion. Access to a more comprehensive data set, including factors such as age, family status, occupation, religious or political convictions, disparities between East and West Germany, or the influence of neighboring countries in border areas could provide further insights into the complex interplay of socioeconomic factors and COVID-19 incidence.

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Payer Perceptions of Nonclinical Value Drivers

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Nonclinical value drivers can constitute important differentiation between therapies from patient experience, economic, or logistical perspectives

European payer and HTA organizations have not historically placed significant weight on nonclinical value drivers, but recent launches demonstrate a potential increase in the consideration of these features

Evolution in the EU may increase the opportunity for these features to be considered in assessments of treatment value

Introduction to Nonclinical Value Drivers

Value assessment processes in Europe are designed to measure the benefit of an emerging therapy based on clinical efficacy, safety, and cost, but less transparent is how European decision makers consider nonclinical benefits that a therapy may offer (eg, route/frequency of administration or treatment setting). Nonclinical value drivers encompass a broad designation of factors that may not directly contribute to clinical or economic evaluation. Although possibly disregarded by health technology assessment (HTA) processes, these nonclinical factors may be meaningful to patients, caregivers, and providers. Nonclinical value drivers may directly or indirectly cause decreased treatment discontinuation rates, lower cost of care (eg, fewer visits to hospital provides savings for the health system, caregiver, and patient), improved patient quality of life, or time savings for caregivers.

Case Studies: Payer Perceptions of Nonclinical Value Drivers

Three recently approved therapies with significant nonclinical benefits were evaluated to provide insight into how these value drivers affect decision making in European HTAs.

Ixazomib (Ninlaro), approved by the European Medicines Agency (EMA) in November 2016, was the first oral proteasome inhibitor (indicated for relapsed/refractory multiple myeloma).¹ In addition to its clinical profile, this nonclinical value driver of an alternative route of administration (RoA) gave ixazomib considerable potential to improve patient convenience during long-term treatment. While payers may not perceive an oral RoA as a benefit, many patients prefer to take an oral pill over an injection or intravenous medication. Additionally, ixazomib's oral RoA allows for it to be administered in the home rather than in the hospital, which can preserve time for the patient and caregiving team, increasing overall productivity.

Despite these benefits, a sample of European HTA assessments of ixazomib

largely focused on clinical outcomes and did not consider the oral RoA as a value driver.¹⁻⁴ There was no mention of the oral RoA in any of the assessed European HTA decisions.

Although possibly disregarded by health technology assessment processes, nonclinical factors may be meaningful to patients, caregivers, and providers.

Although outside of the scope of HTA decisions, one interesting impact of ixazomib's oral RoA was the increased uptake of the regimen during the COVID-19 pandemic. At that time, ixazomib allowed immunocompromised patients with multiple myeloma to avoid visits to the hospital for treatment. This lowered COVID exposure for these patients. As a result, the reduction in use of hospitals during a time of overcrowding and resource allocation also provided an unexpected benefit to the healthcare system. This lowered COVID exposure for patients and reduced the use of hospitals during a time of overcrowding and resource allocation. While this kind of unexpected benefit to the healthcare system is challenging to account for in HTA evaluations, it provides evidence that nonclinical value drivers can have a positive impact on patients and healthcare systems.

Ravulizumab (Ultomiris), approved by the EMA in July 2019, had potential value based on its less frequent administration versus the standard of care.⁵⁻⁸ Ravulizumab was approved for treatment of paroxysmal nocturnal hemoglobinuria based on 2 noninferiority trials versus its predecessor, eculizumab, and is administered through infusion every 8 weeks while eculizumab requires infusions every 2 weeks.

HTA evaluations cited the less frequent administration for ravulizumab versus

eculizumab as a minor advantage from the treatment cost and patient convenience perspectives in the United Kingdom and France.⁵⁻⁶ The National Institute for Health and Care Excellence's (NICE) "recommended with simple discount" decision noted the less frequent dosing schedule versus eculizumab as having the potential to create cost savings. The Haute de Autorité de Santé (HAS) decision of "SMR Important and ASMR IV" in France included mention of expected improvement in care conditions due to the infusion frequency reduction versus eculizumab. Ravulizumab has not yet been evaluated by Spanish or Italian authorities, and the G-BA in Germany did not reference nonclinical drivers in their decisions.⁷⁻⁸

Onasemnogene abeparvovec

(Zolgensma) was evaluated to determine the impact of its one-time administration

schedule. Onasemnogene abeparvovec is the only one-time therapy available for spinal muscular atrophy and was approved by the EMA in 2020 based on a single-arm trial. The orphan-designated gene therapy is indicated for patients born with genetic mutations that cause severe spinal muscular atrophy and is administered via a one-time infusion lasting about 1 hour.






Onasemnogene abeparvovec received favorable HTA outcomes in the United Kingdom, France, and Italy; however, only NICE noted potential benefit from the one-time administration schedule.⁹⁻¹² Specifically, NICE highlighted the reduced need for constant care in the form of monitoring, at-home medical equipment, and invasive treatments, which can be overwhelming for parents and patients with spinal muscular atrophy, although this benefit was not quantified.⁹ HTA bodies in the remaining

countries considered made no mention of nonclinical value drivers in their evaluations, although onasemnogene abeparvovec is not listed in Spain.

Key Trends Across Case Studies

These case studies demonstrate that assessments rarely mention nonclinical value drivers despite hypotheses that: (1) payers may be more likely to consider nonclinical value drivers in disease spaces with high treatment burden (eg, multiple myeloma), and that (2) new technologies which decrease frequency of administration may result in long-term clinical and economic benefits to patients. However, in the 3 instances that nonclinical value drivers were cited in the case-study HTA reports, cost-saving potential or improved quality of life for patient and caregiver were noted, showing that payers may consider nonclinical benefits if they are shown to improve economic or clinical outcomes

HTA Summary of Case Studies

					
Ixazomib in Relapsed / Refractory Multiple Myeloma	Managed Access Through CDF	ODD / Unquantifiable Benefit	SMR: Important ASMR: V	Not Listed	Class C
	No mention of nonclinical value drivers in HTA report	No mention of non-clinical value drivers in HTA report	No mention of non-clinical value drivers in HTA report	N/A	No mention of non-clinical value drivers in HTA report
Ravulizumab in Paroxysmal Nocturnal Hemoglobinuria	Recommended with Simple Discount	No Additional Benefit vs. Eculizumab	SMR: Important ASMR: IV	Not Listed	Class C
	Mention of less frequent dosing schedule vs eculizumab, which may result in cost savings	No mention of non-clinical value drivers in HTA report; costs for eculizumab shown to be EUR 1100-1700 higher	Mention of expected improvement in care conditions due to the infusion frequency reduction vs. eculizumab	N/A	No mention of non-clinical value drivers in HTA report
Onasemnogene Abeparvovec in Spinal Muscular Atrophy	Recommended with Simple Discount	No Additional Benefit vs. Nusinersen (IQWiG)	SMR: Important ASMR: III (Shared with Nusinersen)	Not Listed	Class H
	Potential benefits associated with normal life of patients and caregivers noted	No mention of non-clinical value drivers in HTA report	No mention of non-clinical value drivers in HTA report	N/A	No mention of non-clinical value drivers in HTA report

ASMR indicates Amélioration du Service Médical Rendu; CDF, Cancer Drug Funds; HTA, health technology assessment; IQWiG, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; N/A, not applicable; SMR, Service Médical Rendu.

indirectly. These trends illustrate the potential for nonclinical value drivers to become a greater consideration for European payers due to their potential for downstream impacts.

Impact of Nonclinical Value Drivers From the Patient Voice

One stakeholder group that may be able to increase consideration of nonclinical value drivers are patient advocacy organizations. Formally, patient advocacy organizations may only engage in the HTA process in the United Kingdom, France, and Germany.¹³ In the United Kingdom and Germany, patient advocates take part in the HTA evaluation meetings. In other markets, key opinion leaders included in the clinical review portion of the HTA process are tasked to provide the patient perspective indirectly and advocate on behalf of patients. There is some room for adjusting the HTA evaluation criteria if a nonclinical value driver is deemed important. In Germany, for instance, there is an exemption clause that can grant a therapy that has received a “no added benefit” outcome more flexibility in the reference pricing procedure if key opinion leaders convince the G-BA that it fills an unmet need.

Considering patient input in HTA provides an opportunity for regulators to evaluate nonclinical value drivers on qualitative terms.

Outside of Germany and the United Kingdom, opportunity remains limited for patient advocacy organizations to provide a voice in the HTA process. Developing additional avenues for patients will facilitate access to valuable therapies and provide an avenue for pharmaceutical manufacturers to demonstrate value associated with nonclinical aspects—particularly those that are important to patients.

Considering patient input in HTA provides an opportunity for regulators to evaluate nonclinical value drivers on qualitative terms as opposed to factoring them into quantitative clinical and economic analyses.

Conclusions and Future Outlook

This research shows how the current role for nonclinical value drivers in European HTA decisions is relatively minor—while they are often considered and acknowledged, they are rarely cited as driving decision outcomes. One solution to this oversight may come in the Joint Clinical Assessment, which could provide an opportunity for wider consideration of value drivers. Clinicians and patients will be able to provide input during the Joint Clinical Assessment and Joint Scientific Consultation processes, while patient advocacy organizations will also be able to offer their perspective on nonproduct-related matters, including methodological guidance documents. This is likely to increase the presence and weight of nonclinical value drivers in access decisions in the years to come.

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Distribution Markups and Taxes for Prescription Pharmaceuticals: Do We See the Complete Picture of the Pharmaceutical Price?

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Despite their significant impact on total pharmaceutical spending, pharmaceutical markups and taxes are often neglected in research, policy debate, and public forum discussions.

Regulation of wholesale and retail pharmacy markups should be a balancing act between quality of pharmaceutical provision, incentives in the supply chain, the sustainability of healthcare financing, and patient access to pharmaceuticals.

Taxation of and import duties on pharmaceuticals should be eliminated or be kept to a minimum to improve—rather than discourage—patient access to and affordability of pharmaceuticals, without jeopardizing macro-level fiscal balance.

Introduction

An analysis presented at the ISPOR Europe 2021 conference highlighted considerable variability across countries in how much pharmaceutical markups and taxes contributed to the total cost of pharmaceuticals. From a sample of 35 countries and across 3 selected Anatomical Therapeutic Chemical (ATC) categories (including A10S, L1G, and N3A), pharmaceutical markups and taxes contributed \$8.6 billion (22.3%) and \$2.4 billion (6.2%), respectively, to the \$38.5 billion total expenditure in 2020. In 14% of the countries, markups and taxes had an even higher contribution to the total cost of pharmaceuticals beyond ex-factory level. If the average 22.3% markup had been applied across all countries, a \$2.4 billion saving could have been generated for third-party healthcare payers and patients.

The World Health Organization (WHO) guideline on country pharmaceutical pricing policies¹ contains 10 principles for setting, managing, and influencing the prices of pharmaceutical products (Table). Despite their significant impact on total pharmaceutical spending, 2 principles, notably (1) markup regulation across the pharmaceutical supply and distribution chain and (2) tax exemptions or tax reduction for (prescription) pharmaceutical products, are often

neglected in research, policy debate, and public forum discussions.

The WHO guideline outlines the objectives of national pharmaceutical policies, emphasizing patient access, quality assurance, and rational pharmaceutical use, all of which necessitate a well-functioning pharmaceutical supply system.

Across countries, there are significant differences in the market entry and ownership criteria of retail pharmacies often grounded in history or geography.

The variability in markups and taxes indicates that the global health economics and outcomes research community needs to address the full spectrum of pharmaceutical price regulation and explore the impact of the additional price components and taxes on the final cost that health systems (or patients if health insurance coverage is incomplete or inadequate) will incur.

Retail Pharmacy Sector

Across countries, there are significant differences in the market entry

Table. World Health Organization's principles for setting, managing, and influencing prices of pharmaceutical products

1	External reference pricing
2	Internal reference pricing
3	Value-based pricing
4	Markup regulation across the pharmaceutical supply and distribution chain
5	Promoting price transparency
6	Tendering and negotiation
7	Promoting the use of quality-assured generic and biosimilar medicines
8	Pooled procurement
9	Cost-plus pricing for setting the price of pharmaceutical products
10	Tax exemptions or tax reductions for pharmaceutical products

Bold text indicates relevant principles for distribution markups and taxes

and ownership criteria of retail pharmacies often grounded in history or geography. Additionally, there is a diverse range of markup practices and, consequently, the operational cost of distribution is different, partly based on retail pharmacies' local roles and responsibilities. Over time, there has been a transition to regressive markups and, in some cases, flat fees. In some countries, the retail pharmacy sector has undergone consolidation aiming at increasing efficiency gains for the system under the assumption that horizontal integration could reduce retail distribution markups.² The efficiency gains from this consolidation do not appear to have been translated into health system or patient savings. Still, the optimal proportion of pharmacy markups (compared to the ex-factory price) and the policy implications of different markup approaches remain debated areas.

Certain financial incentives should be considered for pharmacies when implementing specific policies.

Variable distribution markups for different types of pharmaceutical products may be a reasonable approach: for cheaper products, regressive markups could be appropriate; for higher-priced specialty products, flat fees and potentially alternative distribution models could be more suitable, such as the exclusion of traditional retail pharmacies or wholesalers (ie, direct-to-pharmacy) from the distribution system, especially if special transport or delivery is required. Additionally, certain financial incentives should be considered for pharmacies when implementing specific policies. For example, generic substitution could be incentivized through flat markup or dispensing fees for pharmaceuticals with the same active ingredient; equally, additional service fees could be implemented for pharmaceutical care or adherence-enhancing interventions, especially in countries with shortages in primary care professionals.

Lower-income countries (LICs) usually place less emphasis on controlling

pharmacy markups compared to controlling ex-factory prices. Net pharmacy markups may be proportionally higher in LICs than in higher-income countries due to, first, the political and economic imperatives of remunerating domestic retail pharmacies and, second, the widely used confidential price reductions, clawbacks, or payback mechanisms, that are implemented to improve patient access to pharmaceuticals without compromising healthcare system financial sustainability.

Pharmaceutical Wholesaling

In pharmaceutical wholesaling, the public service obligation implies keeping a broad portfolio of pharmaceuticals for common diseases in stock by the largest possible number of traditional full-line wholesalers. However, the emergence of new distribution models, such as the direct-to-pharmacy model, the reduced wholesaler model, or the agency model (ie, where wholesalers become logistics providers on behalf of manufacturers) with a significant home care component, could be observed that may be more suitable for prescription pharmaceuticals requiring special distribution (eg, cold chain).³

Pharmaceutical wholesaling has undergone a significant degree of consolidation in recent years. Horizontal integration may yield modest efficiency gains and, amongst wholesale and retail distribution outlets, may contribute to more significant efficiency gains, resulting in a potential decline in distribution costs. While vertical integration may generate significant efficiency gains, it may also stumble across national regulation, limiting (or altogether forbidding) this from taking place.

There are political incentives to reduce wholesaler markups and discourage vertical integration in those LICs where large wholesalers are international companies rather than domestically owned ones. However, it is also crucial to recognize that meager distribution costs or geographical challenges (eg, large distances) may affect pharmaceutical quality and supply reliability, especially in some LICs.

Overall, in both wholesaling and retailing, there is considerable need to reset policy objectives and implement change, such

as monitoring public prices (rather than ex-factory prices only), pharmaceutical utilization, and proposing changes in markup regulations that reflect the changing market dynamics and the changing nature of newly launched pharmaceutical products. Balancing policy objectives by considering the quality of pharmaceutical provision, incentives in the supply chain, healthcare financial sustainability, and the prevention of catastrophic out-of-pocket spending would be essential in this context.

Taxes and Custom Duties

From a fiscal policy perspective, prescription pharmaceuticals are considered a commodity with specific regulations on consumption taxes, such as value-added tax (VAT), as well as the imposition of import or customs duties.

There is a heterogeneous picture of VAT rates for prescription pharmaceuticals across countries. The macro-level fiscal balance must be considered to determine the impact of taxation on affordability both from health system and patient perspectives, the latter if patients face a significant out-of-pocket burden. In a publicly funded healthcare system, imposing VAT on prescription pharmaceuticals amounts to a stealth tax, depriving health systems from valuable resources by returning these to national treasuries. Upon recognizing this, several countries have implemented reduced or zero-rated VAT on prescription pharmaceuticals.

Lowering or altogether eliminating customs duties would improve patient access to essential pharmaceuticals.

National and international policy organizations recognize the importance of exempting essential health goods (such as prescription pharmaceuticals) and services from VAT and safeguarding equity. This is critical for individual consumers or patients because indirect taxes, such as VAT, are regressive; where patients face significant out-of-pocket costs from prescription pharmaceuticals, VAT may contribute to patients not being able to fill prescriptions, thereby

increasing inequity in access. For a variety of reasons, LICs prefer to raise revenue from indirect (rather than direct) taxation; while this is understandable, based on their revenue-raising capacity, it is not particularly helpful if indirect taxes are imposed in the same blunt manner on prescription pharmaceuticals.

The magnitude of import or customs duties also carries important policy implications, especially in those LICs where most higher priced prescription pharmaceuticals are imported. Lowering or altogether eliminating customs duties would improve patient access to essential pharmaceuticals. This is supported by the European Union's (EU) zero customs duties policy for EU products. Many LICs impose customs duties on finished products to disincentivize their importation, due to favoring import substitution and increasing local content and local manufacturing; this is typically done by subjecting imported active ingredients to zero customs duties. Local manufacturing activity, typically centering on multisource products, continues to drive the need for higher customs duties on imported originator or off-patent branded pharmaceuticals. Again, a balance is needed to ensure that essential pharmaceuticals that cannot be manufactured locally are not subjected to unnecessarily high customs duties that ultimately endanger patient access.

Overall, taxation and customs duty policies should aim to improve rather than discourage patient access and

affordability without jeopardizing macrolevel fiscal balance. To that end, alternative sources for tax revenue could be pursued instead of prescription pharmaceuticals.

Conclusion

Policy debate on fair pharmaceutical prices focuses intensely on ex-factory prices. However, the actual impact on the healthcare system is much higher due to distribution markups and taxation. Besides providing sufficient remuneration for a quality distribution system, markups should be related to the workload and provide incentives for pharmacists in implementing policies (eg, generic substitution, adherence-enhancing interventions). At the same time, due consideration should be given to reducing or eliminating taxes and/or customs duties on prescription pharmaceuticals.

While most EU member states have a detailed regulatory framework for distribution markups, several LICs may lack such mechanisms. It is suboptimal if pharmaceutical distribution markup structures and taxation practices are only based on historical principles or purely fiscal imperatives. There must be consensus on principles and objectives in each setting guided by fairness and equity in patient access, the contribution made by different actors in the pharmaceutical value chain, and an understanding of how regulation reform (including pricing regulation) can lead to optimized performance of distribution practices.

This article is also a call for action on routine data collection and analysis on pharmaceutical cost elements and on facilitating evidence generation on the impact of distribution markup and tax regulation in both higher- and lower-income countries to increase awareness and explore improvements in pharmaceutical care macro-level efficiency.

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International Perspectives on Global Price Transparency

An Interview with Alexander Roediger, MA and Leandro P. Safatle, BS

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Q&A

*In this month's Q&A column, Value & Outcomes Spotlight presents 2 different perspectives on the topic of global price transparency in healthcare. We posed questions to 2 prominent people representing global perspectives and experiences. **Leandro P. Safatle, BS**, economist and researcher at Fiocruz Brasília and former Executive Secretary of the Brazilian Drug Market Regulation Chamber, provides a payer perspective, and **Alexander Roediger, MA**, Executive Director, Global Lead Oncology Policy, MSD in Switzerland provides a manufacturer's perspective.*

The interview elicits interesting viewpoints and examines important considerations for how drug pricing impacts global economies, health policies, and patient access to innovative and life-saving therapies.

“Medicines are not priced according to what it costs to develop them but according to the added value they deliver to patients compared to current standard of care.”
– Alexander Roediger, MA

VOS: The World Health Organization (WHO) has sparked discussions regarding transparent pricing and fair pricing, particularly for low- and middle-income countries (LMICs). What benefits or harms do the “transparent prices” offer? And to whom?

Leandro Safatle: The pharmaceutical industry is research and development (R&D) intensive. It is one of the healthcare sectors that invests the most in innovation. But the high expenditure on R&D alone does not explain the high prices of medicines. There is something more to pricing that goes beyond this type of spending.

The issue of drug price transparency has 2 main sides. The first aspect is the pricing of the drug. The prices in this market have been taking off from the company's cost structure and are tied to other factors that are not very transparent. What are visible are the increase in the payment of cash dividends and the practice of stock buybacks. The low transparency here only benefits the price formation unrelated to the firm's cost structure.

The second aspect is the definition of reference prices by regulatory structures in different countries. Many countries have adopted hidden negotiation practices encouraged by companies so that other countries do not know what the real prices of these products are. Behind this action is the international price comparison tool, adopted as an instrument by the regulatory structures of the countries as a mechanism for greater transparency among prices traded globally. This tool has proven to be one of the main causes of global drug price reductions.

Behind this practice is the promise of lower prices to countries with greater purchasing power if they hide the real prices negotiated with companies. But what we have seen is that the leakage of price references has stimulated the process of financialization of this sector, greatly increasing the trading base prices of these products. The lack of reference causes discounts to occur on top of already inflated prices. What appears to be a discount may not be.

Alexander Roediger: We support transparency in the pricing process for medicines. This guarantees good governance and a fair process. All stakeholders should know how medicines, prices are set.

Many countries or payers negotiate confidential discounts in addition to the list price. The net price after rebate can only be lower than the publicly available manufacturer's price. The call for disclosing rebates assumes that disclosing the net price paid by one country will allow other countries to demand the same price. This assumes that all countries are equal in terms of wealth, population size, and level of healthcare spending, among other important factors. However, we know that this is far from the reality. Economists have shown that affordability is achieved by applying differential pricing (ie, prices that reflect the heterogeneity of countries and their specific conditions and needs [Moon 2020]).

Why are discounts often kept confidential? In some circumstances, discounts are indeed transparent, as different people pay different prices according to their ability to pay (eg, discounts for students' cinema tickets or museum rebates for retired people). This works because the regular cinema visitor accepts paying a higher price; there is a societal consensus in place. Several economists have pointed to the problem of international or external reference pricing (ERP) for medicines. There is no international consensus so that ERP can be applied by any country without restriction. Hence, disclosing rebates results in price convergence towards an average price band that applies to all buyers regardless of their heterogeneity and preferences (Riccaboni 2022; Glynn 2015; Roediger 2019). This means that high-income countries could reap the benefits of affordable prices because the average price is lower than what they can afford. But it also could mean that the average price is above lower-income countries' affordability thresholds, resulting in longer access delays for patients from these countries.

"The price variable is losing its relationship with costs, and what we have seen is that payment of dividends to shareholders is occurring at an even greater magnitude than the increase in R&D spending in this sector." – Leandro P. Safatle, BS

In their 2003 article, [Danzon and Towse](#) noted that confidential rebates play an important role to ensure affordable access: "To achieve appropriate and sustainable price differences will require either that higher-income countries forego trying to 'import' low drug prices from low-income countries through parallel trade and external referencing, or that such practices become less feasible. The most promising approach that would prevent both parallel trade and external referencing is for payers/purchasers on behalf of developing countries to negotiate contracts with companies that include confidential rebates."

The bottom line is that transparency in the price-setting process clarifies the rules of price setting and ensures that the process operates in a fair and transparent manner as outlined by the

"Transparency Directive" (Council Directive 89/105/EEC of 21 December 1988). There is a legitimate interest in ensuring good governance and accountability when public money is used to buy any product or service. But differential pricing is difficult to achieve without an agreement to abolish ERP or to use a framework that allows for confidential rebates.

One way to ensure good governance without undermining greater affordability and delaying patient access has been implemented in Belgium, where members of the Belgian parliament can request that the Court of Auditors review the terms negotiated with a company and report their findings without disclosing the negotiated price or other terms. Belgian law does not call into question the general principle of confidentiality of certain parts of an access agreement (<http://www.ejustice.just.fgov.be/eli/loi/2020/05/04/20202642/justel>).

VOS: Do R&D expenses for novel gene treatment justify their costs? Why are they so expensive and what are the real "value-added" benefits?

LS: The process of financialization of large companies in the pharmaceutical sector is well known. The price variable is losing its relationship with costs, so what we have seen is that dividend payments to shareholders are growing at an even greater magnitude than the increase in R&D spending in this sector. However, scientific advances in the pharmaceutical sector cannot be underestimated. Important technological breakthroughs are indeed taking place and it is necessary to stimulate the advancement and innovations in this sector. Scientific advancements that may have some difficulty in measuring benefits to patients and/or the healthcare system can even open up frontiers for new advances and new treatments. There just needs to be a greater balance to ensure better access to these advances by the population.

AR: I agree that there needs to be a balance between innovation, affordability, and access. Medicines are not priced according to what it costs to develop them but according to the added value they deliver to patients compared to current standard of care. Pricing and reimbursement of medicines is regulated in most countries using rigorous assessment methods to determine their therapeutic value, cost-effectiveness, and budget impact (<https://www.efpia.eu/about-medicines/use-of-medicines/value-of-medicines/>). According to a 2015 survey conducted by the WHO, about 4 out of 5 respondents of a total of 111 reported that their countries had a formal health technology assessment process to assess the value of a new therapeutic (WHO 2015).

The price of novel gene-based treatments is assessed in the same way, considering the additional value they provide and their actual budget impact. These treatments are often used by a very small number of patients, as opposed to treatments used by tens of millions of patients (eg, diabetes, cardiovascular disease, etc). These novel therapies are also revolutionary in that they can cure patients with a single intervention, again contrary to a number of treatment courses that must be taken for life. The cost of these highly specialized therapies also reflects the complexity of administering them (ie, it's not just the cost of the medication but the process of sequencing, developing a solution unique for the patient, maintaining a supply infrastructure, etc). Some of these therapies also generate significant savings to the health system

(eg, when patients suffering from genetic disorders require highly specialized care, life-long interventions, and support). There is also the value any curative treatment brings to society, as patients can live full lives and contribute accordingly.

VOS: Is it possible to negotiate for more affordable medicine costs for LMICs? How does this impact international price referencing by countries?

LS: The drug market is a market full of flaws and is characterized by information asymmetry, low price elasticity due to market demand for the drug, low vertical mobility in the class, loyalty to the brand by the prescriber, complex technical characteristics, and high degree of differentiation and presence of the substitute consumer (credential goods). Credential goods, in turn, can potentially generate asymmetric information, including overtreatment, undertreatment, and overcharging. To contain this type of inefficiency and asymmetries in the market, many governments have created regulatory structures to encourage liability, verifiability, competition, and reputation building. This framework can encourage more affordable pricing practices for LMICs. However, it is important to mention that if the main country of the economy does not reduce these types of market failures, these failures (which have the potential to generate an even greater detachment of prices in relation to their costs) will be imported from that country—in a lesser or greater degree, depending on the regulatory protection system that a particular country creates. The form of international price composition that the country has to deal with is stimulated by the way in which the main economies of the world regulate—or fail to regulate—their markets. This will affect an international equilibrium price.

Finally, to talk about more affordable costs for LMICs, other types of practices can be adopted as well. The regulatory tool is only part of what could be done. There is a whole range of instruments that can stimulate this sector that works as a true economic-industrial health complex (eg, a series of other research, financing, development, production, incorporation, purchase tools, and so forth that can be done regionally or globally, using public and private spheres).

AR: Affordable patient access to medicines takes commitment from a broad set of stakeholders, which is currently lacking as everyone is only trying to improve their own position without necessarily considering the impact on others (win-lose versus win-win). We support pricing according to affordability levels, so-called “differential pricing.” Differential pricing is a good way forward to improve access to medicines. But as noted by Danzon and others and mentioned above, reference pricing and affordable access can be conflicting goals. Therefore, an agreement either to abolish ERP or to create a framework that allows for confidential rebates is necessary.

VOS: Which nations actually profit the most from “hidden” prices?

LS: The experiences of hidden negotiations tend to benefit the technology holder more than the technology-buying country. The discount the country receives tends to generate a price that is likely to be higher than the price generated by a more transparent global market structure. Countries with greater purchasing power, which in theory would use more of this type

of hidden trading practice, would tend to have even lower prices with more transparent practices. Thus, no country really gains from the practice of hidden prices. But poorer countries (which are mere “price takers”) are the most harmed by this type of practice carried out by high-income countries.

AR: Many countries profit, as they negotiate prices and demand confidential rebates. What you call a “hidden price” is what gives payers the flexibility to negotiate a price they can afford and that delivers value for money. A number of economists, such as Danzon and the Organisation for Economic Co-operation and Development, have pointed out the detrimental impact of external reference pricing—which net price transparency can only make worse. In their views, health systems are less likely to get optimal access given their circumstances (including affordability, disease burden, likely clinical practice, etc) if there is a chance that the price they negotiate is referenced and/or misused by other countries with different conditions. Confidential rebates are critical to improve affordability and access.

“Affordable patient access to medicines takes commitment from a broad set of stakeholders, which is currently lacking as everyone is only trying to improve their own position without necessarily considering the impact on others.”
— Alexander Roediger, MA

Differential pricing has been implemented in the case of HIV/AIDS. To ensure global access, companies and governments agreed that HIV treatments be sold to low-income countries at a fraction of the price paid by higher-income countries. Vaccines are sold at highly reduced, confidential prices to intermediaries (eg, Pan American Health Organization & Gavi, the Vaccine Alliance) for LMICs. Even within Europe, if a reasonably secure mechanism exists to keep discounted prices confidential in lower-income countries, companies have offered that their products be priced according to each country's ability to pay. The European Federation of Pharmaceutical Industries and Associations, together with other stakeholders, has just recently proposed a mechanism for EU countries (see <https://www.efpia.eu/media/636854/ebtp-efpia-discussion-document-slides.pdf>).

VOS: Describe the European Union’s “Transparency Directive” and its implications.

LS: The Transparency Directive aims to ensure transparency of information for investors through a regular flow of regulated information disclosures and the dissemination of such information to the public. The requested information is related to the Market Abuse Directive and is also related to the directive on transparency of decisions that regulate prices and reimbursement of medicines in EU countries. The search for greater transparency comes from the need to reduce informational asymmetries and make these markets work in the best way without widespread committing abuses of a dominant position.

AR: Directive 89/105/EEC (<https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A31989L0105>), commonly referred to as the “Transparency Directive,” was adopted in 1989. It aims to ensure the transparency of the procedures established by EU Member States to control the prices and reimbursements of medicinal products. The Transparency Directive does not affect national policies on price setting and on the determination of social security schemes, except as far as it is necessary to attain transparency objectives.

The Transparency Directive lays down 4 major requirements with respect to individual pricing and reimbursement decisions:

- 1) *Timeliness*: Decisions must be made within a specific timeframe (90/180 days)
- 2) *Transparency*: Criteria for pricing and reimbursement decisions must be transparent
- 3) *Objectivity*: Decisions must be communicated to the applicant and contain a statement of reasons based on objective and verifiable criteria
- 4) *Due process*: Decisions must be open to judicial appeal at a national level

The Transparency Directive shall ensure that price setting operates in a fair and transparent manner across the European Union. Nevertheless, despite the Directive, pricing and reimbursement decisions differ greatly between countries in the European Union. Patients in Germany wait around 133 days to access new medicines compared to patients in Romania that endure a wait of more than 899 days. (<https://www.efpia.eu/news-events/the-efpia-view/efpia-news/shortening-the-wait-patient-access-to-medicines-in-europe>)

VOS: How will medical innovation be impacted by regulating drug prices?

LS: The market for innovative medicines follows a more global, than national, pricing logic. Prices tend to be set first in markets such as the United States because of the combination of a lack of regulation in this market and high payment capacity. This combination is ideal in markets full of failures such as drug products that maximize price increases and maximum revenue extraction. It is natural for companies to then look for countries where this combination also exists.

This type of situation ends up segmenting the market and, mainly, segmenting spending on innovations. Classes of drugs that achieve greater profitability by extracting the greatest possible global value attract greater spending on innovation. This directs the focus of spending on innovations by the largest companies in this sector. Companies are focused on innovating more and more in these segments to the detriment of innovations that could bring greater social benefits. In short, the lack of drug market regulation in the United States ends up affecting the global market. Today, the lack of regulation in the US market propagates market failures and informational asymmetries around the world, inflating the price of these innovations and bringing a financial logic to the price formation of this sector.

AR: Pricing and reimbursement regulations are signals for innovators. The EU Orphan Regulation No 141/2000 led to the development of 142 orphan medicines by 2017; in 2010, there were only between 15 and 70 medicines, depending on the definition (see: https://health.ec.europa.eu/medicinal-products/medicines-children/evaluation-medicines-rare-diseases-and-children-legislation_en#:~:text=Final%20study%20report%20and%20executive%20summary). The opposite example is antibiotics.

Policies also have an impact on patients. The Belgium Pact for the Future and the Italian Innovation Fund have accelerated the time to patient access and made new medicines available faster (Lawlor 2021). At the same time, other policies may delay access.

In the end, policy making in health is not straightforward but rather the challenge to keep the right balance of different goals. According to the OECD, governments have 3 main objectives: (1) making treatments accessible, (2) ensuring that healthcare remains affordable and sustainable, and (3) securing future innovation (OECD, 2017). These objectives may conflict with each other. It is everyone's responsibility to find the right balance.



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