SEPTEMBER/OCTOBER 2021 VOL. 7, NO. 5

VALUE & OUTCOMES SPOTLIGHT

A magazine for the global HEOR community.

Wearables: Making a Mark in Digital Health

ISPOR
Improving healthcare decisions

VALUE & OUTCOMES
SPOTLIGHT

SEPTEMBER/OCTOBER 2021
VOL. 7, NO. 5

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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.

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FROM THE EDITOR

Wearable technology has come a long way from the mechanical pedometer, an unreliable, inaccurate, and clunky device first introduced in the 1920s. Today, a wide variety of precise, lightweight, and multifunctional electronic and digital devices are available including watches, eyewear, earbuds, rings, and many more that—among other functions—measure our activity and collect biometric data. Whether tracking the number of steps walked or calories burned, heart rate, oxygen saturation, sleep patterns, blood pressure, glucose, or medication adherence, users of these devices are generating and capturing data in real time that provide valuable insights into their health and wellbeing outside of traditional physician visits. These patient-generated data help to fill the gap between those visits and provide a more holistic view of patient health. This additional data and monitoring should, in turn, improve medical decision making and lead to better health and patient outcomes. Tracking and capturing such data can also support payers in making reimbursement decisions by filling in data gaps and reducing uncertainty.

Empowering patients and involving them in the collection of their own health data creates a sense of accountability, responsibility, and ownership of their healthcare. This active patient engagement can lead to improved health habits, improved patient outcomes, and potentially greater cost savings. The collection and ownership of their data engenders a more motivated and educated patient who can proactively identify potential medical concerns or issues s/he may be facing and seek professional help more quickly to address them. Proactivity of this sort may lead to earlier diagnoses and treatments that can only further improve patient outcomes. For example, elderly patients can benefit from the use of these devices in measuring blood pressure, reporting falls, creating medications alerts, and other health- and safety-related data. Patients in low- and middle-income countries and rural and remote locations can also benefit from these technologies by gaining access to improved health services through telehealth and capturing their own patient-generated data that can be remotely transferred to a centralized location for analysis.

Currently over 350,000 health apps are available that are often paired with wearables to provide digital data to various stakeholders such as patients, caregivers, and providers for optimization of care and treatment. Despite the many benefits of wearables, multiple challenges and barriers for and in their use exist, including clinical appropriateness of outcomes, accuracy and validity, access issues arising from the cost of wearables, data management, limited standards and guidelines, and data security. As an example, in this issue, Stephen M. Schueller discusses navigation of the digital mental health landscape using *One Mind PsyberGuide*, a resource that helps individuals through product reviews that capture credibility, user experience, and transparency around data security and privacy.

As the digital health field continues to evolve and become more mainstream, health economics and outcomes research will be essential in addressing these challenges and demonstrating—with evidence—whether these digital devices improve patient outcomes, expand access, and/or reduce healthcare utilization and costs.

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

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

ISPOR SPEAKS

Advancing HEOR in Low- and Middle-Income Countries: How ISPOR Makes an Impact on Global Health

Robert Selby, MBA, Director, Global Networks, ISPOR, Lawrenceville, NJ, USA

ISPOR's Strategic Plan 2024 affirms a strong commitment to support the core tenets of the Society's mission even amid unprecedented challenges caused by the COVID-19 pandemic. The Society's mission of improving healthcare decisions around the globe remains more critical than ever.

As part of the strategic plan priorities, the ISPOR Board of Directors acknowledged the elevation of advancement and utilization of health economics and outcomes research (HEOR) in low- and middle-income countries (LMICs).

Per the World Bank, LMICs are countries with gross national incomes (GNI) that range from $1045 or less (low income); $1046 to $4095 GNI per capita (lower-middle income); and $4096 to $12,695 GNI per capita (upper-middle income) (**Figure 1**). Many countries lack resources to invest adequately in healthcare spending and are more vulnerable to shocks posed by crises such as the global pandemic. At the same time, LMICs stand to benefit greatly from HEOR as they address issues of access and budget, among others.

Figure 1. Low- to middle-income countries classification defined by the World Bank (July 2021).

Low-Income Countries ($1045 or less)	Lower-Middle Income Countries ($1046 to $4095)		Upper-Middle Income Countries ($4096 to $12,695)	
Afghanistan	Angola	Lesotho	Albania	Kazakhstan
Burkina Faso	Algeria	Mauritania	American Samoa	Kosovo
Burundi	Bangladesh	Micronesia, Fed. Sts.	Argentina	Lebanon
Central African Republic	Belize	Mongolia	Armenia	Libya
Chad	Benin	Morocco	Azerbaijan	Malaysia
Congo, Dem. Rep	Bhutan	Myanmar	Belarus	Maldives
Eritrea	Bolivia	Nepal	Bosnia and Herzegovina	Marshall Islands
Ethiopia	Cabo Verde	Nicaragua	Botswana	Mauritius
Gambia, The	Cambodia	Nigeria	Brazil	Mexico
Guinea	Cameroon	Pakistan	Bulgaria	Moldova
Guinea-Bissau	Comoros	Papua New Guinea	China	Montenegro
Korea, Dem. People's Rep	Congo, Rep.	Philippines	Colombia	Namibia
Liberia	Côte d'Ivoire	Samoa	Costa Rica	North Macedonia
Madagascar	Djibouti	São Tomé and Principe	Cuba	Panama
Malawi	Egypt, Arab Rep.	Senegal	Dominica	Paraguay
Mali	El Salvador	Solomon Islands	Dominican Republic	Peru
Mozambique	Eswatini	Sri Lanka	Equatorial Guinea	Romania
Niger	Ghana	Tanzania	Ecuador	Russian Federation
Rwanda	Haiti	Tajikistan	Fiji	Serbia
Sierra Leone	Honduras	Timor-Leste	Gabon	South Africa
Somalia	India	Tunisia	Georgia	St. Lucia
South Sudan	Indonesia	Ukraine	Grenada	St. Vincent and the Grenadines
Sudan	Iran, Islamic Rep	Uzbekistan	Guatemala	Suriname
Syrian Arab Republic	Kenya	Vanuatu	Guyana	Thailand
Togo	Kiribati	Vietnam	Iraq	Tonga
Uganda	Kyrgyz Republic	West Bank and Gaza	Jamaica	Turkey
Yemen, Rep.	Lao PDR	Zambia	Jordan	Turkmenistan
		Zimbabwe		Tuvalu

ISPOR Activities That Support LMICs

Since its early days, ISPOR has invested resources in advancing HEOR and supporting members working and residing in LMICs, allocating $2.7 million toward mission-focused initiatives and carrying through those investments into 2020 and beyond.

ISPOR's portfolio of programs supporting LMICs includes complimentary memberships and fee-waived registrations and educational grants to enable selected member attendance at ISPOR events. To support the work of chapters, chapter educational funds are offered and complimentary educational webinars and publications, leadership training, and stakeholder roundtables (including patient, health technology assessment, and payer roundtables) are conducted. Activities organized by ISPOR global groups including regional consortia and networks and chapters also facilitate information sharing and capacity building (**Table**).

ISPOR is also strongly committed to leadership development and scientific excellence recognition globally and has recently introduced the LMIC Health Economics and Outcomes Research Award to recognize individuals with demonstrated outstanding research achievements in HEOR in LMICs. This award helps to support and acknowledge outstanding HEOR work underway in LMICs. To learn more about ISPOR's mission support programs for LMICs, please visit here.

These programs have had a direct impact on ISPOR's mission to improve health globally by providing key

Table. ISPOR low- to middle-income countries programs.

Membership Fee Waivers	ISPOR offers membership fee waivers to individuals from LMICs to support capacity building, career advancement, and enrichment of the society's member community.
ISPOR Conference Travel Grants	Application-based travel grants to ISPOR conferences support the development of local research and foster information sharing to advance the field of HEOR.
Chapter Educational Funds	ISPOR regional chapters from LMICs can apply for financial support through the ISPOR educational fund to facilitate local educational activities and discussions with government and other decision makers.
Regional Publications	ISPOR publishes a scientific journal, *Value in Health Regional Issues*, to offer a publishing platform for researchers from emerging regions to advance the science globally. ISPOR also publishes a free quarterly regional newsletter, *ISPOR News Across*, to share the latest policy trends and HEOR news from around the globe.
Awards and Recognition	ISPOR recognizes members and thought leaders in HEOR through a wide variety of scientific achievement and leadership awards and research presentation awards, including the *Value in Health Regional Issues* Excellent Article Award, the Outstanding Regional Chapter Award, and the LMIC Health Economics and Outcomes Research Award.
Training and Education	ISPOR supports capacity building through short courses, educational webinars, leadership training, and HTA training.
ISPOR Global Groups	ISPOR global groups (including regional consortia, networks, and chapters) serve as platforms for education, information-sharing, career development, research collaboration, and networking to advance HEOR globally.
Regional Roundtables	ISPOR stakeholder roundtables provide a forum for global healthcare stakeholders (including HTA assessors, payers, regulators, and patient representatives) to interact and engage in discussion on key issues.

HEOR indicates health economics and outcomes research; HTA, health technology assessment

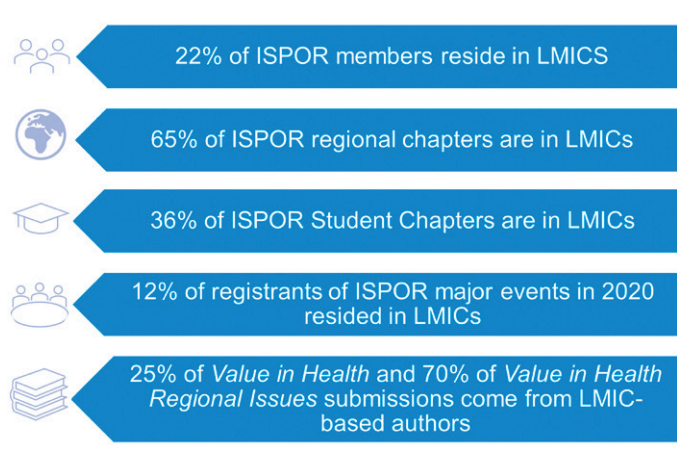
opportunities for professionals to share their research and interact with fellow experts to further their careers, fostering inclusivity and diversity of thought within the HEOR profession. LMIC investments further allow HEOR to thrive in emerging regions by building capacity and awareness within the specific countries. These efforts also indirectly support countries in the development of their health systems and economies to improve resource prioritization, access to health technologies, investment and innovation, and opportunities for growth to improve health outcomes and standards of living.

These efforts, coupled with the growing need for HEOR globally, have ensured that individuals from LMICs make significant contribution to major ISPOR initiatives (**Figure 2**).

ISPOR regional chapters and members demonstrated a significant impact on global health policy in 2020 through their activities:

- Chapter members in China participated in PE/HTA (pharmacoeconomic/health technology assessment) appraisal for the national health insurance negotiation with manufacturers and served on the PE Expert Panel to update the 2020 National Medical Insurance Medication List.
- In Malaysia, chapter members conducted a postpandemic COVID-19 analysis organized by the Academy of Science, Ministry of Science and Technology.
- In Thailand, key chapter members were included in an economic working group to support the selection of the National List of Essential Medicines of Thailand.

Figure 2. Contribution to ISPOR initiatives by individuals from low- to middle-income countries (LMICs).

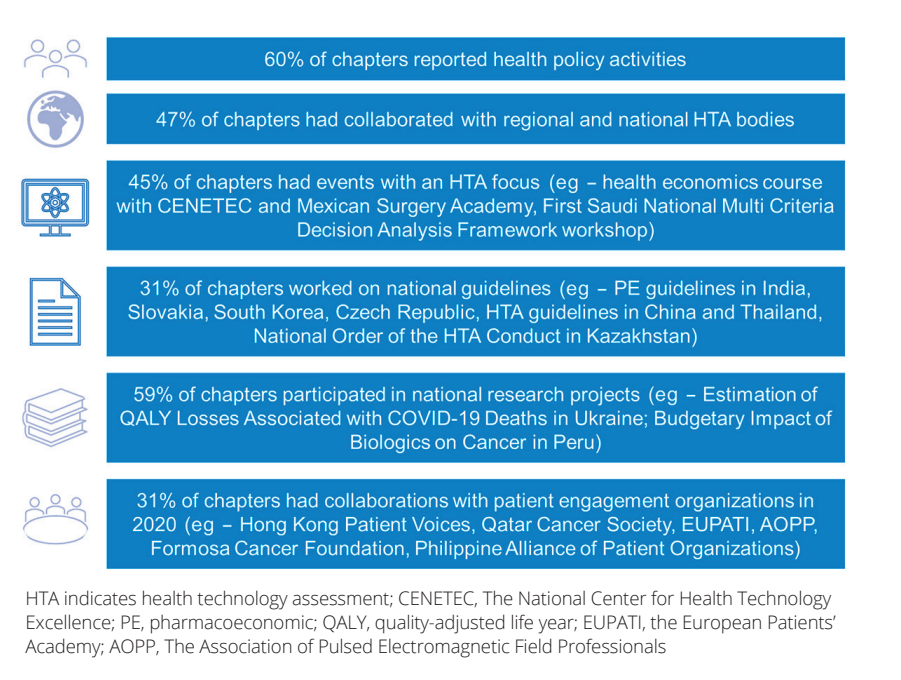


- In Ukraine, chapter members and national HEOR leaders have been involved the Ministry of Health's HTA working group and participated in the development of HTA legislation. More examples of impact are listed in **Figure 3**.

Raising Visibility and Impact: The ISPOR LMIC Initiative

While the success and impact of these programs is evident through these outcomes, it has also been acknowledged by ISPOR leaders and members that broad awareness of these programs and of their impact is lacking. This is an important consideration as ISPOR develops key performance indicators to objectively measure investments and their impact and success.

Figure 3. ISPOR Regional chapter impact on health policy in 2020.



HTA indicates health technology assessment; CENETEC, The National Center for Health Technology Excellence; PE, pharmacoeconomic; QALY, quality-adjusted life year; EUPATI, the European Patients' Academy; AOPP, The Association of Pulsed Electromagnetic Field Professionals

Two separate ISPOR Board of Directors work groups recently affirmed that ISPOR groups and chapters are doing significant work and that more can be done to highlight results that may go unnoticed by the broader ISPOR membership.

To assess strategy and progress, the ISPOR Board of Directors appointed a special LMIC work group in early 2021 with the goals of (1) evaluating ISPOR's impact in LMICs to achieve the mission to promote HEOR excellence to improve decision making for health globally; and (2) assessing the return on current investments and recommending adjustments to current plans, proposing strategies to best elevate ISPOR's impact.

The results from the work group generated a final proposal for action:

- Develop a communication plan to share the academic and health policy impact of ISPOR in the LMICs
- Explore collaboration opportunities with select organizations on LMIC-related initiatives
- Articulate key performance indicators around measures of success for ISPOR LMIC programs

Looking to the future, program objectives will be balanced between 2 facets of impact—policy and academic—with an overall view to improving healthcare decision making. ISPOR will also develop a communication plan to share the impact of ISPOR's LMIC program within the ISPOR membership and the broader HEOR and healthcare community. As part of the communication plan, impact stories and testimonials from key membership demographics will be collected to spotlight the impact that ISPOR has had on the community from a member perspective. Finally, ISPOR will explore collaboration opportunities with select organizations on some LMIC-related initiatives. Key ISPOR leadership groups, including the LMIC work group and global councils, will be working with ISPOR staff through 2022 and beyond to implement these proposal objectives.

We Welcome Your Input!

As ISPOR looks to capture the member story and illustrate the great progress and influence being made at the local level, we encourage you to share your stories of impact with us and describe how ISPOR has helped to advance your career and the field of HEOR in your country. As part of the rich tapestry that is our ISPOR membership community, you are integral to the success of our mission.

We encourage you to get actively involved in our global initiatives, even if you are not from the LMIC regions. Contact globalnetworks@ispor.org to learn more.

HEOR NEWS

1 V-Safe: How Everyday People Help the Centers for Disease Control Track COVID-19 Vaccine Safety With Their Phones (Kaiser Health News)

The program, created to complement the Centers for Disease Control's vaccine monitoring system, has enrolled more than 9 million people so far to share information about their health since getting the shot.
Read more.

2 The White House Wants $65 Billion for an "Apollo-Style" Pandemic Preparedness Program (STAT News)

The Biden administration's sweeping new biosecurity plan would represent one of the largest investments in public health in American history.
Read more.

3 External Control Arms and Debunking Real-World Data Myths (pharmaphorum)

External control arms based on real-world data have been slow in gaining traction and clarity is needed about how they can bring therapies to patients faster.
Read more.

4 Cancer Research Faces Uncertain Post-COVID-19 Landscape (Deep Dive Magazine)

Paul Workman, the Institute of Cancer Research, London, says the UK government has to implement a clear plan for funding and development going forward to ensure a bright future for cancer research.
Read more.

5 American's Health Insurance Plans Asks for "Good Faith Safe Harbor" With Surprise Billing Rule (Becker's Hospital Review)

The health insurance lobby, America's Health Insurance Plans, wants government officials to put into a place a "good faith safe harbor" as well as accommodations through 2023 to adjust to the upcoming surprising billing rule.
Read more.

6 Japan Set to Issue "Vaccine Passports" Online by Year-End (Asahi Shimbun)

For Japanese residents who are fully inoculated against COVID-19 and are planning to travel overseas, the government is planning to issue digital "vaccine passports."
Read more.

7 The 10 Power Players to Watch on Democrats' Drug Pricing Push (STAT News)

Senate Finance Chair Ron Wyden (D-Ore), Senate Majority Leader Chuck Schumer (D-NY), and Sen. Bob Menendez (D-NJ) are among the key players of note in the upcoming efforts to reform drug pricing.
Read more.

8 Are Vaccine Selfies Good or Bad for Fighting Hesitancy? Researchers Weigh In (Becker's Hospital Review)

Research published recently in *Psychology & Health* says social media selfies of people getting their COVID-19 shots could help spread the message of vaccine safety and effectiveness.
Read more.

9 China Allows Couples Third Child Amid Demographic Crisis (Asahi Shimbun)

The amendment to the Population and Family Planning law is intended to stem off a demographic crisis that threatens the country's future prosperity.
Read more.

10 Swapping Salt for Substitute Cuts Rates of Stroke, Heart Attack and Death, Study Finds (South China Morning Post)

A 5-year study in rural China found that substituting table salt with alternatives containing less sodium and more potassium reduces the incidence of stroke, heart attack, and death.
Read more.

FROM THE JOURNALS

Can Machine Learning Be Used to Predict Patients' Hospital Reentry Rates?

Section Editors: **Soraya Azmi, MBBS, MPH**, Beigene, USA; **Agnes Benedict, MSc, MA**, Evidera, Budapest, Hungary
Guest Contributor: **Elizabeth Zimmerman**, University of Washington, Seattle, WA, USA

How Good Is Machine Learning in Predicting All-Cause 30-Day Hospital Readmission? Evidence From Administrative Data

Li Q, Yao X, Échevin D

***Value Health*. 2020;23(10):1307–1315**
doi.org/10.1016/j.jval.2020.06.009

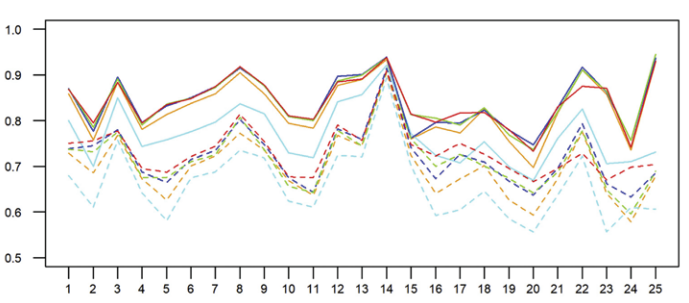
Hospital readmissions account for a significant part of overall inpatient expenditures and have considerable clinical and economic effects on patients and society. In addition, there are ongoing connections between hospital readmission rates and patients' ages, comorbidities, diagnostics, and lengths of stay. Thus, readmission is a difficulty that all hospital systems need to address. Understanding these outcomes, such as readmission rates, requires data availability, explanatory variables, and observations. Data are gathered through administrative and electronic medical records, as well as several other significant data sources. Machine-learning algorithms can be used to detect complicated patterns and interactions in data when there are unknown and sophisticated risk factor correlation patterns. While identifying individuals at risk of readmission is only the first step toward reducing rehospitalization, machine learning can improve predictability.

There are various ways to analyze data, whether using traditional statistical methods or more recent machine learning algorithms. The paper by Li et al highlighted the novel approach of analysis using machine learning algorithms. The purpose of analysis can be prediction as opposed to uncovering clinically meaningful explanatory variables. In this instance, the authors explored machine learning's predictive capacity and effectiveness using Canadian hospitalization records. The specific objective focused on predicting 30-day readmission using the algorithms while comparing the results to traditional approaches.

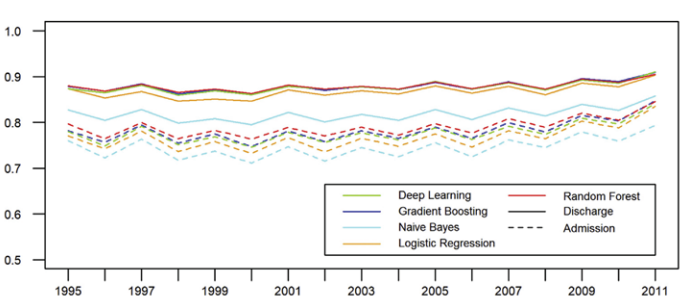
Using administrative data from 1,631,611 patient visits from 1995-2012 in Quebec, the likelihood of rehospitalization and discharge was estimated. The methods behind the study included records of hospital stays based on prior admission diagnoses (MED-ECHO) and billed medical services and physician compensation (RAMQ). The performance of statistical methods including Naive Bayes, traditional logistic regression, and logistic regression with penalization (ie, methods that discourage the model from having extremely unrealistic values) was used to predict patient reentry. This was compared to the machine learning methods such as random forest, deep learning, and extreme gradient boosting. The authors split the data set into 2 sections to train the machine learning algorithm: training data and testing data. The split-sample method allowed the testing of multiple algorithms while avoiding over-fitting. The machine learning process was undertaken by the algorithms using a training dataset (which contained 80% of the data) over 10-fold validation attempts. Finally, the trained model calculated the study results using a separate hold-out dataset (20% of the data).

To compare the results of the approaches, the primary measure used was the area under the receiver operating characteristic curve (AUC). The AUC is a commonly used prediction metric to assess discriminative ability. An AUC of 0.5 implies that the model performs no better than chance; an AUC of 0.7 to 0.8 shows that the model has modest to adequate discriminative capacity, and an AUC greater than 0.8 shows that the model has high discriminative performance. Study results showed the AUC was over 0.79 at admission and greater than 0.88 at discharge. For example, deep learning achieved 0.7898, and logistic regression with penalization achieved 0.7759. However, Naive Bayes performed significantly worse. At hospital discharge, extreme gradient boosting was the most predictive algorithm; random forest and deep learning also achieved better than 0.88 in AUC; and logistic regression with penalization reaching greater than 0.87 in AUC. The **Figure** depicts

Figure. (A) Area under the receiver operating characteristic curve by major diagnostic category.



(B) Area under the receiver operating characteristic curve by discharge year.



AUC variation across key diagnostic categories and the pattern of variation is similar among algorithms. Logistic regression with penalization produced comparable results; however, standard logistic regression failed without penalization. The importance of explanatory variables fluctuates depending on the algorithm and calibration curves that ensured the data's precision. In general, the Naive Bayes method is the quickest in machine learning. Furthermore, it was discovered that logistic regression with penalization had a comparable processing speed. The authors noticed that when they evaluated the 3 empirical approaches, extreme gradient boosting required substantially less time than the other 2. Outcomes further explain that the diagnostic codes, which divide into multiple subcategories, are highly predictive markers.

According to the authors' research, predictions may be beneficial when machine learning is used, and findings indicate that it may be capable of predicting 30-day readmissions. This study could be an exciting read for those looking to learn more about utilizing machine learning to forecast readmissions and reduce rehospitalization. The extra costs that each additional readmission to the hospital brings for any countries or payers' healthcare system could be further reduced. Attempts to anticipate this critical cost driver of reentry rates have shown modest to moderate results in the past. With further investigation, the findings and forecasts presented here show that machine learning could, in the future, be used to aid decision making by identifying the risk factors of readmissions putting the patient's well-being front and center.

RESEARCH ROUNDUP

Section Editor: **George Papadopoulos, GradDipEpi**, Lucid Health Consulting and University of New South Wales, Sydney, NSW, Australia

Guest Contributor: **Aakash Bipin Gandhi, BPharm**, ISPOR Student Network Chair, 2019-2020, University of Maryland, Baltimore, MD, USA

Challenges for the Evaluation of Digital Health Solutions—a Call For Innovative Evidence Generation Approaches

Guo C, Ashrafian H, Ghafur S, Fontana G, Gardner C, Prime M. *NPJ Digit Med*. 2020:3(1):110. pubmed.ncbi.nlm.nih.gov/32904379/

Summary

Digital health holds great potential for offering favorable healthcare solutions to cater to ever-changing patient needs. Digital health solutions include, but are not limited to, mobile applications, wearable devices such as smart watches and fitness bands, and telehealth services. Digital health has rapidly evolved over the past 2 decades. For example, 200 health applications are added to the market daily with a total of 300,000 health applications currently in existence. In contrast, there is a lack of concurrent growth in the generation of cost-effective and credible evaluation methodologies that can help determine whether digital health products are effective and compliant with set regulatory standards. Traditional approaches for the evaluation of digital health solutions include expert opinion, surveys and interviews, retrospective observational studies, or randomized controlled trials. However, these evaluation techniques are costly and time-consuming. Approaches such as computational or clinical simulation may offer a potential solution. For example, computational simulation can be used for the verification and validation of software components that make up a digital product. Clinical simulation has been previously documented to help develop and evaluate digital health tools. Further, a prior study evaluated standardized responses from primary care physicians who interacted with professional patient actors through video appointments that were based on simulated clinical scenarios. These responses were used to create a clinical decision support tool that can help inform treatment decisions for patients at the time of care.

Relevance

Creators of innovative digital health products may face hurdles regarding the generation of suitable evidence to support their approval and use. Techniques such as simulation methodologies may encourage innovators to pursue development of digital health products due to their low cost and time-saving features as opposed to traditional techniques that incur high costs and are time-consuming.

Advancing Digital Health: FDA Innovation During COVID-19

Kadakia K, Patel B, Shah A. *NPJ Digit Med*. 2020;3(1):161. nature.com/articles/s41746-020-00371-7

Summary

During the COVID-19 pandemic, the US Food and Drug Administration (FDA) approved temporary policies to continue supporting the development of digital health solutions through the relaxation of regulatory requirements surrounding these products. For example, the FDA announced that it would not limit the adoption and distribution of digital health solutions that support mental health care such as computerized behavioral therapy or mental health-related mobile health applications for the duration of the state of emergency due to the pandemic. Normally, these digital health solutions would require premarket notification submissions to the FDA under the Federal Food, Drug, and Cosmetic Act, among other regulatory specifications. Further, this would help ensure continued access to suitable digital solutions that help alleviate the adverse effects of mental health conditions that have taken a toll on the population as result of the pandemic. In relation to chronic healthcare conditions, the FDA announced that it would not be opposed to nonsignificant modifications that may result in an alteration to indications, claims, or functionality associated with digital blood pressure measurement instruments or similar noninvasive digital remote monitoring devices. Improved accessibility to these devices can help prevent an increase of in-person clinical visits for associated services and in turn decrease the risk of spreading the COVID-19 infection.

Relevance

This article highlights the need and significance of flexibilities for regulatory requirements associated with digital health products, especially considering the long-lasting impact the pandemic may have on population healthcare systems. The article stresses that specific guidelines related to such efforts should be included in a country's pandemic preparedness and recovery plan in order to ensure that access to and evolution of innovative technologies such as digital health products is not hindered.

Virtual ISPOR Conferences and Events

Signal

October 26 | 11:00AM – 12:00PM EDT

Venture Capital Investment: Upstream Decision Making on Value in Healthcare

Guest Speakers:

- Vineeta Agarwala, MD, PhD, General Partner, Andreessen Horowitz, San Francisco, CA, USA
- Tom Cassels, President, Rock Health and General Manager of Rock Health's Advisory Services, San Francisco, CA, USA
- Alyssa Jaffee, Partner, 7wire Ventures, Chicago, IL, USA

November 11 | 10:00AM - 11:15AM EST

Live at the ISPOR Europe 2021 Preconference Summit, Copenhagen, Denmark

Healthcare Decision-Making 4.0: Danish Approach

Host :

- Tove Holm-Larsen, CEO, Pharma Evidence, Copenhagen, Denmark

Speaker:

- Niels Christian Ganderup, Senior Investment Manager – HealthTech and Data, Copenhagen Capacity Investment Agency, Copenhagen, Denmark

Co-Discussants:

- Ulrik Niels Lassen, Head, Department of Oncology, Rigshospitalet Chair, Steering Committee, OSCAR Project, Copenhagen, Denmark
- Kenneth Forsstrom Jensen, Strategic Market Access Manager, Roche Denmark, Co-Chair, Steering Committee, OSCAR Project, Copenhagen, Denmark

The ***Signal*** series—ISPOR's signature program—looks beyond today's linear thinking to explore topics that will shape healthcare decision making over the next decade. ***Signal*** episodes are scheduled throughout the year and feature conversations with speakers who are innovative thought leaders and change makers in both healthcare and other sectors of economy, science disciplines, and areas of human inquiry that can impact healthcare.

Learn more and register at www.ispor.org/signal

The conversation begins on Twitter #ISPORSignal

Virtual ISPOR Education

Virtual ISPOR Short Courses

October 13-14 | 10:00AM – 12:00PM EST (2 hours per day)

Introduction to Health Economics and Outcomes Research

***Presented in Spanish with English portions translated to Spanish.*

What you will learn in this introductory-level course:

- How to incorporate health economics into study design and data analysis
- How to collect and calculate the costs of different healthcare or healthcare economic evaluation alternative treatments
- How to determine the economic impact of clinical outcomes
- How to identify, track, and assign costs to different types of healthcare resources used

October 20-21 | 8:00AM – 10:00AM EST (2 hours per day)

Introduction to Patient Engagement in Medical-Product Research

What you will learn in this introductory-level course:

- What patient engagement is, its historical context, and its significance throughout ISPOR's HEOR taxonomy
- How to plan, implement, and differentiate among tools needed for meaningful patient engagement activities
- Best practices and practical solutions for real-world examples

November 3-4 | 10:00AM – 12:00PM EST (2 hours per day)

Selecting Rapid Review Methods for Health Technology Assessment

What you will learn in this intermediate-level course:

- Approaches to undertaking a rapid review
- Skills for selecting appropriate rapid review methods

November 10 | 9:00AM – 1:30PM EST

Use of Propensity Scores in Observational Studies of Treatment Effects

What you will learn in this intermediate-level course:

- How propensity scores can be used to mitigate confounding through standard observational approaches
- Advantages and disadvantages of standard adjustment relative to propensity score-based methods
- Propensity score methodology and use of risk adjustment models relative to propensity scores

continued on next page >

Virtual ISPOR Short Courses, continued

November 16-17 / 11:00AM – 1:00PM EST

Budget Impact Analysis for Health Decision Making in Latin America

***Presented in Spanish with English portions translated to Spanish.*

What you will learn in this intermediate-level course:

- The main concepts, elements, and discussions on budget impact analysis (BIA) for health decision making in the context of Latin American countries
- Conceptual aspects of the BIA of a new healthcare technology
- The relevance of BIA for decision making in coverage policies in the regional context
- Primary methodological recommendations for a BIA in Latin American countries

December 7-9 / 10:00AM - 12:00PM EST

Budget Impact Analysis II: Applications and Design Issues

What you will learn in this intermediate-level course:

- The 6-step approach for developing budget impact analyses
- Static vs dynamic budget impact models
- Device and diagnostic technologies
- Realistic features such as patient copayments and use of generics
- Good practices for building budget impact models

December 13-14 / 10:00AM – 12:00PM EST

Cost-Effectiveness Analysis Alongside Clinical Trials

***Presented in Spanish with English portions translated to Spanish.*

What you will learn in this introductory-level course:

- Trial design, selecting data elements, database design and management, analysis, and reporting of results
- Trials designed to evaluate effectiveness (rather than efficacy), as well as clinical outcome measures
- Ways to obtain health resource use and health state utilities directly from study subjects and economic data collection
- Analyses guided by an analysis plan and hypotheses

December 15-16 / 10:00AM - 12:00PM EST

Going Beyond the Standard: Exploring Advanced Survival Modeling Techniques for Immuno-Oncology

What you will learn in this intermediate-level course:

- Identify survival modeling techniques most appropriate in a specific context
- Learn how modeling choices propagate into health economic evaluations

ISPOR Short Courses are designed to enhance knowledge and techniques in core health economics and outcomes research topics as well as emerging trends in the field. Short courses offer 4 or 8 hours of premium scientific education and an electronic course book. Active attendee participation combined with our expert faculty creates an immersive and impactful virtual learning experience. Short courses are not recorded and are only available during the live broadcast.

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October 28	*1PM EDT*	**Addressing Prenatal Exposures and Outcomes for Regulatory Requirements Using Real-World Data** *Sponsored and Presented by* IBM Watson Health
November 18	*10AM EST*	**External Control Arms – The Case for a Standardized Lexicon and Toolkit** *Sponsored and Presented by* Certara Evidence and Access
November 18	*11AM EST*	**Real-World Insights into the US COVID-19 Crisis: New Findings from Analyses of Claims Data** *Sponsored and Presented by* Syneos Health
November 18	*12PM EST*	**Demonstrating the Value of Vaccines: Global NITAG and HTA Requirements** *Sponsored and Presented by* PRMA Consulting
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Wearables: Making a Mark in Digital Health

The wearable devices market is expected to grow at a compound annual growth rate of 18% from now until 2026.[1] While interest in wearables may have originated in consumer-oriented wellness products, increasing interest in health applications, especially during the current COVID-19 pandemic, is driving market growth. In addition, wearables' miniaturization, reliability, and accuracy are expanding possible healthcare use cases.

Susannah Fox, former Chief Technology Officer at the US Department of Health and Human Services; Laurie Orlov, founder of Aging and Health Technology Watch; Dave Albert, MD, founder and Chief Medical Officer, AliveCor; Vivian Lee, MD, PhD, MBA, President, Health Platforms, Verily Life Sciences; and Jessica Mega, MD, MPH, cofounder and Chief Medical and Scientific Officer, Verily Life Sciences, shared their thoughts on the current wearables market, how these devices are changing research, and how health economics and outcomes research may support this growth.

The Changing Nature of Wearables

The first wearable devices or "wearables" arrived in the 1920s when a British man named John Harwood was awarded the first patent for a pedometer. Today, wearables refer to small electronic mobile sensors incorporated into daily wear items (watches, eyewear, earbuds, rings) that collect biometric or activity data (**Table 1**).

These devices capture a broad array of patient-generated health data: vital sign measurements (heart rate, skin temperature), physical activity (steps, duration of movement), sleep patterns, continuous glucose monitoring, and health events such as falls, strokes, and atrial fibrillation. In addition, new devices are in development to detect depression and other mental health conditions. Wearables are often paired with a companion smartphone app allowing patients, providers, or other stakeholders to review data on health trends and events.

Evolving Use Cases for Wearables

Wearable devices have the potential to collect large quantities of continuous patient-generated health data in real time—data that could inform clinical decision making and provide earlier diagnoses. For years, wearables have provided consumers with the activity data needed to reach their health goals such as weight reduction or blood pressure management.

Wearables can deliver important "between visit" data to providers, offering critical insight into a patient's specific treatment response and health status. Not only can these devices assess whether a product is working as intended, but they can also alert case management of health events that may warrant intervention.

Table 1. Types of wearable sensors and targeted measurements.

SENSOR	MEASUREMENT
Activity	
Accelerometer	Step count Impact force Speed Sedentary time Exercise
Barometer	Stair count
Biometric	
Photoplethysmogram	Heart rate Cuffless blood pressure Oxygen saturation Cardiac output Stroke volume Pulse-based rhythm detection Sleep
Electrocardiogram	Monitoring interval measurements
Oscillometry	Wrist cuff blood pressure
Other	
Biochemical sensors	Invasive: continuous blood glucose, electrolyte monitoring Noninvasive: sweat and saliva electrolytes and hydration status
Biomechanical sensors (ballistocardiograms, seismocardiograms)	Cardiac output, stroke volume, lung fluid volume, body vibrations, weigh

> Wearables may help fill this data gap, providing the additional evidence payers need to determine whether the clinically proven outcomes demonstrated in clinical trials are observed within their population.

With the expanded use of telehealth due to COVID-19, wearable data allow remote providers to diagnose and monitor these patients. They have also enabled the smooth continuation of managing clinical trial patients by enabling trial participants to provide their trial data without a face-to-face visit.

Wearables could also become the foundation for some outcomes-based agreements, providing payers with additional data to support reimbursement. Payers must often make reimbursement decisions with incomplete information. Small clinical trial populations, short-term data due to accelerated approval, suboptimal outcomes measures, and other data gaps create uncertainty for payers. Orphan drugs for rare diseases (especially in pediatric populations), high-cost curative therapies, and conditions with high unmet need often enter the market with limited data to reassure payers that these therapies can achieve clinically meaningful improvements in the payer's population. Wearables may help fill this data gap, providing the additional evidence payers need to determine whether the clinically proven outcomes demonstrated in clinical trials are observed within their population.

The Growing Influence of Consumers

The use of wearable devices has more than tripled in the past 4 years,[2] bringing new products and manufacturers into the market. While consumer electronics companies have dominated the wearables market, new and expanding opportunities for wearables in health services and clinical trials have led to a growing presence of healthcare and device companies. **Table 2** lists some of the key companies currently in this market.

Miniaturization Leading to More Use Cases

Thanks to higher quality, consumer-grade sensors, wearables continue to shrink in size, expanding their possible uses. For example, new smart patches can measure temperature, heart rate, blood sugar, and other vital statistics as (or more) effectively than other wearable technologies. They can also remotely administer medication, such as insulin for diabetic patients.

The performance gap between medical- and nonmedical-grade wearables is closing with improved sensor accuracy potentially expanding opportunities for these miniaturized devices. And with advances in miniaturization enabling device makers to integrate sensors into discrete, nearly invisible wearables, patient acceptance may also increase.

Table 2. Wearables 2021: Top products, producers.

Watches		
Apple Watch	Apple	HR, PA, sleep, falls, ECG, blood oxygen saturation (Series 6)
Fitbit Flex, One, Charge	Fitbit	HR, PA, sleep
Vivoactive, Vivofit, Forerunner	Garmin	HR, PA, sleep
HeartGuide	Omron Healthcare	BP (oscillometric BP monitor), PA
Patches		
iRhythm	Zio Patch	HR, ECG
Preventice Solutions	BodyGuardian	HR, ECG
Corventis Inc.	Nuvant MCT	HR, ECG
Wearable Biosensor	Philips	HR, PA, RR, temperature
Bands		
Microsoft Band	Microsoft	HR, PA, sleep
Halo	Amazon	HR, PA, skin temperature, sleep, voice tone Halo uses the phone's camera to create a 3D body image to monitor body change and body fat percentage.
Rings		
Oura Ring	Oura	HR, PA, sleep
Miscellaneous		
KardiaMobile	AliveCor	HR, single-lead and 6-lead ECG
Freestyle Libre	Abbott	Continuous blood glucose monitoring
BioHarness 3 clothing	Zephyr	HR, PA
Polar H7 strap	Polar	HR, PA

BP indicates blood pressure, ECG, electrocardiogram, HR heart rate, PA, physical activity, RR, resting rate.

Putting Data in Patients' Hands

The popularity of consumer electronics means millions of individuals now own the technology that can help them engage more fully in personal health monitoring. For example, a 2019 Pew Research Center study found that 21% of US adults surveyed reported regularly wearing a smartwatch or fitness tracker.[3] By 2022, more than 1 billion wearables are expected to be in use globally.[4]

Wearables place patients at the center of their health data-collection process. Continuous tracking of activity levels, sleep patterns, heart rate, or even body temperature could motivate patients to improve their health habits. While patients have traditionally taken a more reactive approach to their health (pursuing care when they feel sick or in pain), new wearable devices can now alert patients of potential concerns. And as more patients gain access to their real-time health data, better health outcomes may be on the horizon for millions of patients.

Susannah Fox, former Chief Technology Officer, the US Department of Health and Human Services, Washington, DC, USA has long focused her research on how people use emerging technologies to pursue diagnoses and advocate for treatment. She supports the growing use of wearables, especially their role in furthering the citizen science or community science movement.

Fox noted that wearables support the possibility of "N of One" studies where individuals can solve their health questions. "Wearables can be very useful tools for people who have a theory about their health." She views these individuals as pioneers, many of whom are in the rare disease space, engaging in "peer-to-peer healthcare" and sharing insights built from their data. Fox noted such initiatives are not new, with 14 past Nobel Prize winners having been "self-experimenters," seven of whom won prizes for their work.

In her view, these pioneers are not unlike other tech innovators. "What they're doing now is going to be widespread in 5 or 10 years." Given the initiatives these early adopters have shown in their use of wearables, Fox hopes business leaders and policy makers follow the pioneers and support their collaborative approach to health data.

Fox acknowledged, however, the spectrum of accuracy among these tools. Currently, clear guidance regarding which apps gain featured promotion remains limited and consumer popularity seems to take precedence ***(see related piece, "Navigating the Digital Mental Health Landscape: One Mind PsyberGuide" published elsewhere in this issue)***. As a result, she proposes some third-party validity tests instead of the current approach whereby citizen scientists do those validity tests themselves.

However, Fox applauds the work of these pioneers as they break new ground for large entities (pharmaceutical companies, other healthcare companies) to follow.

Engaging Older Patients

While wearables with actionable health information can help motivate individuals and help patients gain control over their health, they are only effective when worn. Although wearables' data could prove valuable in helping older patients manage chronic conditions to identify health events, the wearable market for older adults is in its infancy. Recent data show wearable acceptance among older individuals lags far behind that of younger citizens.

Wearables place patients at the center of their health data-collection process. Continuous tracking of activity levels, sleep patterns, heart rate, or even body temperature could motivate patients to improve their health habits.

Laurie Orlov, founder of the blogspot, "Aging and Health Technology Watch", is a strong proponent of wearable use in older adults. She recently published, "The Future of Wearables and Older Adults 2021," in which she reviewed the benefits wearables offer older patients and the challenges of expanding adoption within this population.[5]

Orlov sees significant value in wearables as monitoring devices for older adults and in their ability to supply data needed to refine treatment decisions and avoid possible over-medication of these patients. For example, she recounted how patients who experience office anxieties might have elevated blood pressure recordings during an office visit. These elevated readings could result in medications prescribed at dosages higher than may be necessary. By providing potentially more accurate trend data, wearables may improve prescribing practices.

> "Most of the progress in this space is happening outside the hospital and outside the doctors' practices, driven by consumer tech companies."
> – Laurie Orlov

She believes wearables may help detect disease progression at an early stage, possibly avoiding health events and related costs. For example, wearables could reveal early onset stroke symptoms or detect disease progression. Orlov highlighted how wearables might benefit patients with Parkinson's disease, detecting changes in their condition outside infrequent clinic visits. Also, wearables might soon be able to identify early dementia symptoms or alert providers of a patient's fall.

However, Orlov notes wearables only benefit patients when used consistently and correctly. As yet, acceptance of these devices among older adults has been slow. She notes that wearable markets, particularly for older adults, are in their infancy with only 20% of that segment of the population routinely using them, according to AARP.[5]

> "We are generating mountains of data. We don't know what's important yet clinically."
> – David Albert, MD

She suggested some of this delay may be due to design issues, such as a small user interface compared to a smartphone. Older users may struggle to read status updates on their wearable devices. In addition, alerts may be too quiet for patients to hear. Consumers are already familiar with voice-based devices in consumer products, so incorporating voice-based activity into health wearables may be a possible remedy for difficult-to-read interfaces. Nevertheless, Orlov hopes that as design improves, wearables will become a standard part of the daily lives of older adults.

"As the data become available and validated, there will be more interest in wearables," said Orlov. "For example, today there are studies underway comparing the efficacy of care for a person with a wearable and without a wearable."

Orlov noted the importance of consumer electronics companies. "Most of the progress in this space is happening outside the hospital and outside the doctors' practices, driven by consumer tech companies."

Finding Clinical Value in Mountains of Data

A crucial part of improving patient outcomes is timely clinical intervention. High-quality patient-generated health data may provide early indications of worsening health. However, navigating through the mountains of trend data created by wearables remains challenging.

Dave Albert, MD, founder and Chief Medical Officer, AliveCor, Mountainview, CA, USA recognizes that we are in the early days of turning data into clinically meaningful insights and actions. But he notes that research shows that monitoring drug effects with wearables could improve clinical outcomes and reduce costs.

Albert recounted a recent study by Labreck, et al, that demonstrated how wearables could reduce health services utilization and costs among patients starting sotalol (a class III antiarrhythmic).[6] Given sotalol's risk of QT prolongation, the US Food and Drug Administration requires monitoring new patients in an inpatient setting. However, with hospital capacity strained due to COVID-19, inpatient monitoring of patients during sotalol loading places an undue burden on hospital resources. The authors reported that the average sotalol loading cost of patients monitored with an AliveCor Kardia® wearable device in an outpatient setting was significantly lower than patients undergoing inpatient loading ($886.30 versus $7571.76, P <0.001). Said Albert, "We might be improving clinical outcomes, but we also might be improving financial outcomes. And that's good for the patient and everybody else."

> "We might be improving clinical outcomes, but we also might be improving financial outcomes. And that's good for the patient and everybody else."
> – David Albert, MD

He highlighted another significant benefit of expanded use of these products; improved access to health services. Wearables may help patients in remote or underserved regions receive ongoing medical care without hospitalization.

Albert noted that to improve patient outcomes, the artificial intelligence within the devices must perform with diagnostic sensitivity, specificity, and predictive accuracy (positive and negative). However, he emphasized that multiple stakeholders hold wearable producers, such as AliveCor, to high performance standards. "We are validated not only by the regulatory bodies but by the clinicians themselves."

Empowering Patients as Coproducers of Health

Vivian Lee, MD, PhD, MBA, President, Health Platforms, Verily Life Sciences, Boston, MA, USA, sees wearables redefining how we view health outcomes. She notes that health outcomes have been defined traditionally by measures having more to do with processes than clinical states, such as administrative claims data. "They have very little input from the patients themselves," she said.

She argues that wearables can change this approach to defining health outcomes. "Now we have a completely different way of thinking about health outcomes and about the quality of health measured. Not in terms of these processes or checklists (Did we avoid an infection? Did we avoid something bad happening to you?), but in terms that are meaningful to the individual patients. How is their quality of life? Are they able to engage in the activities that they want to engage in? Have they been able to lose the weight? Or manage their blood pressure? Or get through a pregnancy?"

Data obtained from wearables can help researchers better understand the substratification of disease state, perhaps detecting differences by age, gender, or race. This information could advance more personalized treatment options for patients.

She also sees wearables changing how we view health production. "We were trained in medical school that we, as doctors, were primarily responsible for your health." She continued, "While in some settings, such as operating rooms, the doctor is mostly producing your health. But for most of the things that matter in our health, most takes place outside of the hospital or clinic: how you exercise, what you eat, how you sleep, your ability to comply with medications."

Wearables and related software help individuals engage and coproduce their own health. "I think (this) is a fundamental mind shift that we're seeing that we're just participating in the earliest stages now."

Providing a Nuanced View of Health and Health Outcomes

Jessica Mega, MD, MPH, cofounder and Chief Medical and Scientific Officer, Verily Life Sciences, Boston, MA, USA sees wearables as providing a more nuanced view of health outcomes. To Mega, these devices allow the capture of both the quantitative and qualitative aspects of many conditions. As an example, Mega noted that wearables might capture 2 different aspects: duration and quality of sleep. Or for Parkinson's patients, wearables might quantify different parts of movement: the number of steps and the quality of ambulation.

> "I think that the health economics world can really help us quantify the impact that guides and directs this transformation."
> – Vivian Lee, MD, PhD, MBA

Mega emphasized the importance of wearables data in helping researchers to observe variation within health outcomes, providing a more refined view of the disease state. She noted treatment standards often focus on an average disease profile. But she emphasized that what is really important is the individual patient's experience and how things are changing over time. Mega sees access to trending patient-generated health data as critical to understanding an individual's health status.

Mega also credits wearable data with helping researchers understand the diversity within a disease. "If we start to get more input, then we can substratify." In addition, these data can lead to better treatment decisions. "That's good for the outcomes of that patient," she said. "And it's good for how we essentially pay for healthcare."

> "These data can lead to better treatment decisions. That's good for the outcomes of that patient and it's good for how we essentially pay for healthcare."
> – Jessica Mega MD, MPH

But she also credits these devices with improving patients' engagement in their care. Even though these tools are often viewed as a one-way data transfer, they are also a way to connect more broadly. She noted clinical trial participants also experienced heightened engagement when outfitted with wearable devices. For example, during the COVID-19 pandemic lockdown, clinical trial participants were often unable to attend in-person visits necessary for clinical study monitoring. "We saw higher participant engagement than we had expected during a pandemic," Mega said. "People continue to want to stay involved with any assessments they could do remotely."

Mega added, "I think the idea of bridging what happens in clinics with what happens 365 days out of the year is going to be incredibly powerful, both in research and care."

Impediments to Acceptance

Despite the tremendous value wearable devices may provide to patients, providers, and payers, wearables still face barriers to acceptance.

These include:

- ***Accuracy and validity.*** The absence of clear regulatory oversight policies governing commercial wearable devices has led to the emergence of wearables of unknown safety and efficacy. Inaccurate data may be more harmful than no data.
- ***Meaningful use criteria and clinical evidence.*** Few trials have examined the superiority of wearables for clinical outcomes as compared with no wearables.
- ***Hardware cost and coverage.*** Cost of wearables may lead to access issues and exacerbate health disparities.
- ***Data security.*** Patient-generated health data may be subject to breaches.
- ***Data management.*** Challenges with data interoperability.

How HEOR May Help

Many contributors reiterated the importance of health economics and outcomes research (HEOR) researchers in overcoming these impediments. Albert welcomes HEOR professionals to the wearables world, noting "researchers will be important in validating and verifying the claims made true that the outcomes actually improve."

Lee concurred, "I think that the health economics world can really help us quantify the impact that guides and directs this transformation." She added, "We should be challenging digital technology entrepreneurs and innovators to think about how we actually innovate in the payment space to drive these businesses, to deliver services that really improve value for the individual in that way that we talk about in healthcare, and really improve health outcomes and manage reasonable patient expectations."

Looking Ahead

These products have the potential to change how we deliver and pay for care. But to achieve this goal, HEOR is needed to determine whether these devices truly meet the goals of improving health outcomes, while expanding access and reducing health services utilization.

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By the Numbers: Digital Health/Wearables

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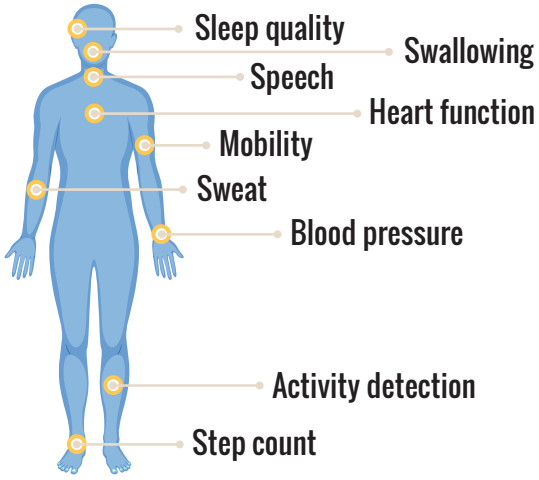
Most Frequent Types of Data Harnessed From Digital Wearables and Applications[1-4]

Most Common Conditions Managed With Wearables:
- Respiratory diseases
- Weight management
- Metabolic diseases
- Cardiovascular diseases
- Pain
- Stress
- Seizures

Main Types of Data From Wearables That Are Already Harnessed:
- Physical activity
- Circadian rhythm
- Sleep
- Skin temperature
- Glucose monitoring
- Seizure onset
- Medication adherence



Top Companies Producing Digital Wearables Based on 2021 Market Share[5]

Apple	Xiaomi	Samsung	Huawei	BoAt
29%	11%	10%	8%	3%

How Wearables Will Change How We Measure Outcomes[6,7]

Opportunities
- Improved measurement objectivity
- Increased frequency of capture and data volume
- Decreased collection burden for patient and provider
- Real-world data in varying settings
- Improved data fluidity

Challenges
- Clinical appropriateness of outcomes
- Limited ability to measure psychosocial outcomes
- Quality dependent on correct use of DHT*
- Variability between populations
- Limited standards and guidelines

**digital health technology*

References available online.

Navigating the Digital Mental Health Landscape: One Mind PsyberGuide

Stephen M. Schueller, University of California Irvine, Irvine, CA, USA; Executive Director, One Mind PsyberGuide, Napa, CA, USA

Digital health is a rapidly growing area. As it stands, over 350,000 health apps exist and over 90,000 of those apps were added in 2020 alone.[1] Mental health is an important and growing segment of this market. The COVID-19 pandemic has resulted in both an increased need for scalable mental health solutions and an increased interest in digital solutions. Venture capital investments in mental health start-ups rose 72.6% from Q1 2020 to Q1 2021, totaling $2.4 billion in 2020 and accounting for 19% of all digital health funding.[2] Despite there being over 10,000 mental health apps, little guidance is available to help consumers. In the United States, very few products have pursued and received clearance from the US Food and Drug Administration (FDA). In fact, the FDA relaxed regulations in light of the COVID-19 pandemic, which allows for products to market themselves to consumers without FDA approval or clearance.[3] As such, we need frameworks and resources to support the evaluation of digital mental health solutions and to provide this information to consumers in useful ways.

> A consumer might be okay with their data being shared with a third party as long as they find value in the product, whereas a practitioner might be unwilling to recommend a product that shares any information with outside parties.

One Mind PsyberGuide is a nonprofit project that aims to help people to use technology to live mentally healthier lives. Started in 2013, One Mind PsyberGuide conducts evaluations of digital mental health products, especially mental health apps. To date, One Mind PsyberGuide has reviewed over 460 digital mental health products. The major outputs of One Mind PsyberGuide are product reviews comprising evaluations of 3 metrics: (1) credibility, (2) user experience, and (3) transparency around data security and privacy practices, and also provides professional reviews that give additional background and describe the use case for the product. (**Figure**)

One Mind PsyberGuide uses these 3 metrics rather than an overall total score such as a percentage or a 5-star rating, because we believe there is no "magic number" for digital mental health products. Different things will work for different people and similarly, people might weight or consider factors differently. For example, a tech-savvy 20-something might be willing to tolerate a product with a more difficult learning curve when it comes to user experience as long as it is effective. A consumer might be okay with their data being shared with a third party as long as they find value in the product, whereas a practitioner might be unwilling to recommend a product that shares any information with outside parties. Providing these metrics separately allows consumers to make individual decisions based on their needs and resources. As such, each evaluation metric is intended to be able to answer a question a consumer might have when considering using a specific digital mental health product:

- Credibility: How likely is it that this app can do what it says it can?
- User experience: How likely is it that I will actually use this app?
- Transparency: What happens to the data I enter into this app?

We describe each of these metrics below in more detail and provide some lessons learned from our 8 years of reviewing products in the digital mental health space.

Figure. Evaluation metrics used to look at mental health apps.

One Mind PsyberGuide Evaluation Metrics

Credibility: How likely is it that this app can do what it says it can?

Digital mental health products make a range of claims such as treating depression, boosting well-being, increasing focus, or decreasing stress. The vast majority of these claims are unsupported. Only about 3%-5% of digital mental health products are evidence-based.[4] Even those that are evidence-based have rarely been rigorously evaluated through methods such as randomized controlled trials. Instead, most rely on indirect research evidence, that is, they digitize a previously validated evidence-based intervention or practice.

The One Mind PsyberGuide credibility metric is intended to quantify the support for an app including the direct and indirect research evidence, as well as other aspects of the development team and processes. The credibility metric has 4 components: (1) research, (2) development, (3) intervention specificity, and (4) consumer ratings. The research subscore evaluates the amount of research evidence for a product as well as the degree of independence and review of data collected in that research. The highest scores are provided to products with at least 2 rigorous research evaluations such as a randomized controlled trial with findings that have been published with peer review, and involved funding or collaboration from nonprofit sources or outside investigators. The development subscore evaluates

The highest scores are provided to products with at least 2 rigorous research evaluations such as a randomized controlled trial with findings that have been published with peer review and involved funding or collaboration from nonprofit sources or outside investigators.

inclusion of developmental processes incorporating stakeholder engagement and early feedback such as design, feasibility, and acceptability data, the inclusion of clinical input on development, credibility of the development team gained from past evidence-based products, and ongoing maintenance of the product. The intervention specificity subscale looks at the clarity of the proposed goal of the intervention and whether it is clear, measurable, and specific. Lastly, the consumer ratings subscale considers the number and average value of app store reviews.

User Experience: How likely is it that I will actually use this app?

A major challenge facing digital mental health products is lack of engagement and long-term sustainment. Most apps that are downloaded are never opened and digital mental health is no exception.[5] The user experience and usability of an app impacts which apps people start to use and differentiates those that would be used long-term and those that would be quickly discarded. One Mind PsyberGuide uses the Mobile App Rating Scale created by Stonyanov and colleagues[6] to evaluate an app's user experience and usability.

The Mobile App Rating Scale evaluates 4 components of user experience: (1) engagement, (2) functionality, (3) aesthetics, and (4) information quality. Each component is evaluated using 3 to 8 questions each rated on a 5-point scale with well-defined anchors. These scores are averaged, producing scores that range from 1.0 to 5.0. In general, a 3.0 on the Mobile App Rating Scale is considered average, and a 4.0 is considered good. Of all the products currently reviewed on One Mind PsyberGuide about 41% have received Mobile App Rating Scales greater than 4.0. Although the products reviewed might be selected in ways that mean this is not fully representative of the market at large.

Transparency: What happens to the data I enter into this app?

People want to know that their private data are secure and protected when they are interacting with mobile apps. This is especially important when dealing with sensitive information related to mental health. One Mind PsyberGuide conducts an evaluation of data security and privacy policies using our transparency metric. We refer to it as a transparency metric, rather than data security and privacy itself, because we review the policies provided by developers, rather than a technical audit of the app. This is useful to consumers as privacy policies are rarely consumer-friendly. They are long, contain technical jargon, and are written at high literacy levels. Furthermore, consumers might not appreciate all the information they should consider when reviewing a policy and guidance conforming to standards are useful.

Our transparency scale was developed by reviewing privacy policies of various apps and aligning these with clinical, ethical, and industry standards. We initially tested our transparency scale on a set of 116 mobile apps for depression.[7] We found that only 49% of those apps even had privacy policies and that only 4% received an acceptable rating on our scale. Similar reviews have demonstrated the poor data security and privacy practices of many mental health apps.[8]

Lessons Learned From Practice

One Mind PsyberGuide has been operational for over 8 years, and in those 8 years we've learned several lessons relevant to the evaluation of digital mental health products and dissemination of information to consumers. People are interested in using digital tools to support their mental health and want high-quality solutions that they can trust. As such, the information provided by One Mind PsyberGuide fills an important gap in the current digital health ecosystem. The most popular content on our website, in terms of how people find our site and which pages they visit, are our professional reviews. These professional reviews are narrative reviews that describe the background, use case, and pros/cons of individual products.

A major challenge facing digital mental health products is lack of engagement and long-term sustainment.

We have also found that our credibility metric and user experience metric are not correlated, demonstrating that many of the evidence-based products—those developed by academic

teams with expertise in clinical evaluation—do not have a good user experience and that many of the most engaging products—those developed by industry team with expertise in product design—often lack clinical evidence. Increasingly, industry teams are bringing on clinical and research expertise, but their contributions to the clinical evidence base in this space is still limited. Nevertheless, there is a desire for credible information to help guide decision making in this space.

Conclusion

Digital mental health is a large and rapidly growing area. At the same time this area has advanced with little regulation or guidance, resulting in a "Wild West" for consumers and purchasers. One Mind PsyberGuide is one resource to help navigate this area, providing evaluations of credibility, user experience, and transparency around data security and privacy.

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Can We Demonstrate the Value of Next-Generation Sequencing Approaches Within Traditional Value Frameworks?

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Existing value frameworks do not adequately address the value of testing approaches from all healthcare system stakeholder perspectives.

There is a need for greater transparency and harmonization in approaches used for NGS testing evaluation and decision making.

The current course of healthcare is unsustainable, and 20%-40% of healthcare resources are wasted.

Introduction

During Virtual ISPOR Europe in Milan, a forum was convened that looked at the question, "Can we demonstrate the value of next-generation diagnostic testing approaches within traditional value frameworks?" which included next-generation sequencing-based testing approaches from reimbursement, ecosystem, and public health perspectives.

The current course of healthcare is unsustainable (**Figure**),[1-4] and according to the World Health Organization (WHO) and the Organization for Economic Cooperation and Development, 20%-40% of healthcare resources are wasted.[5]

The transformation of healthcare towards precision medicine—giving the right patient the right treatment at the right time[6]—has the potential to put healthcare on a more sustainable path. Emerging data suggest that multigene next-generation sequencing (NGS)-based testing approaches enable more efficient use of healthcare resources through testing, treatment, and reduction in hospitalization.[7-9] When it comes to precision medicine, there is currently a lack of clarity and consensus on a global level on how to assess the value of the technologies and services of precision medicine. In this article, there will be a focus on the challenges of NGS testing approaches as a core element of precision medicine, using mainly US data because most published information is currently available there.

The ISPOR Forum addressed the broader context of next-generation testing (NGT) approaches, which is used as an umbrella term, and covers testing approaches such as multigene NGS, comprehensive genomic profiling, and others (see **Table** for select examples of multigene NGS tests). Oncology is one of the most advanced medical fields in which molecularly guided treatment options have repeatedly demonstrated delivering better outcomes for patients, and multigene NGS plays an important role in identifying the right patient for

Figure. Unsustainable course of healthcare.

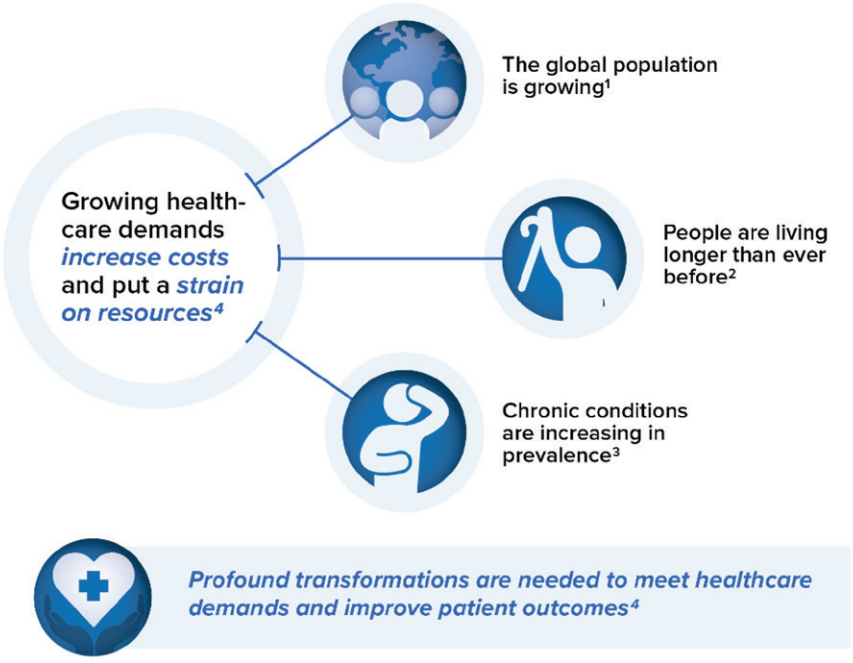

Table. Examples of multigene NGS tests utilized in current clinical practice.

NGS Test	Test Description	Example: Clinical Scenario
Whole exome sequencing[6]	Test on a person's blood or buccal cell DNA to sequence a person's whole exome via NGS platform	Children with neurodevelopmental disorders such as epilepsy and/or severe intellectual disabilities with no definitive genetic diagnosis despite prior targeted genetic testing
Multigene liquid biopsy testing[7]	Test on a patient's blood sample to sequence circulating tumor DNA present in the blood via NGS platform	Patients with solid tumors such as those with advanced non-small lung cancer who are contraindicated for invasive tumor biopsy
Rapid whole-genome sequencing[10]	Accelerated test on a patient's blood sample to sequence a person's whole genome in a few days via NGS	Critically ill infants with immediate life-threatening disorders of likely genetic origin

the right treatment.[11] The number of cancer drugs that need biomarker testing has increased continuously since the late 1990s. This trend is ongoing, so increasingly research and development (R&D) is investigating tumor-agnostic biomarkers (mutations that appear in tumors across indications). Currently, there are over 75 tumor-agnostic treatments in R&D pipelines.[12]

> The current course of healthcare is unsustainable and according to the World Health Organization and the Organization for Economic Cooperation and Development, 20%-40% of healthcare resources are wasted.

Emerging data suggest that multigene NGS approaches enable more efficient use of healthcare resources through testing, treatment, and reduction in hospitalization.[8,9,13] This is important in the context of the current unsustainable course of healthcare spending and existing budget constraints (see **Figure**).

From a physician's perspective, the value of NGS-based testing lies in the information that it provides for making quicker and better diagnostic and treatment decisions (ie, which treatments to use or to NOT use, because of resistant mutations[3] and clinical trial options, etc).[4] Molecular tumor boards have proven to play an important role in interpretation of information as well as enabling efficient healthcare delivery for patients to be treated with options for which there is enough evidence available.[3]

From a precision public health perspective, the focus is on using data to improve health and achieve social justice—equity, social inclusion, and empowerment. The value of NGS-based testing and similar approaches from a population health perspective is giving the right intervention to the right population at the right time, which is consistent with supporting an individualized treatment approach. Therefore, it contributes to improving the health of identified populations, even if at first glance individualized medicine and public health seem to be in conflict.[14] From the outset there were 2 camps: (1) public health and precision medicine present a false dichotomy, since improving population health should include healthcare and molecular tools to stratify populations into risk groups to provide more efficient and effective prevention and treatment strategies, and (2) a more traditional public health view of whole population health that is determined by far more than healthcare. In conclusion, population health outcomes reflect the combined influences of multiple biological and social health determinants, public health efforts and medical care, making "both zip codes and genetic codes" important for health.[15]

The core concern of the traditional public health view is whether healthcare system investments in precision medicine's targeted clinical interventions would come at the expense of existing public health measures that could have a greater impact on population health, and their need for resources. As paradoxical as it seems, while precision medicine focuses on individualized care, its success truly requires a population-based approach.

Value Framework for NGS Testing

Value frameworks, whether utilized explicitly or implicitly in access decisions, have traditionally focused on the payer perspective and are used to assess the value of clinical outcomes of new therapies relative to current therapies. They should help to better inform decisions.[16] This assessment sometimes involves evaluating the combination of a test and treatment. Several challenges have been raised in assessing the value of diagnostic approaches, including NGS, when limited to these traditional elements, particularly as the results of multigene NGS testing often provide an end to a prolonged diagnostic odyssey, which may potentially derive from (1) identifying or ruling out one or more potential treatment approaches/further clinical intervention, and/or (2) achieving a definitive diagnosis or ruling out one or more suspected diagnoses. Broadly, the utility of all such information provided by multigene NGS and other testing approaches may be referred to as the "value of knowing," a healthcare concept introduced decades ago in the literature but formalized more recently in the HEOR field.[17,18] Yet when applying a standardized framework, it is important to first consider who the decision maker is, since value may be defined and assessed differently, depending on perspective.

There exist a variety of different value frameworks; some are more centered around medical evidence (eg, National Comprehensive Cancer Network,

American Society of Clinical Oncology, European Society for Medical Oncology); others are payer-centered (eg, Institute for Clinical and Economic Review, National Institute for Health and Care Excellence); and some are specific to precision medicine (eg, Personalized Medicine Coalition, MedTech Europe, Genomic Medicine Integrative Research Framework). There is also an ISPOR Value Framework that expands the elements of value beyond traditional cost-effectiveness by incorporating novel value elements like the value of knowing (diagnostic odyssey), real option value (opportunity to benefit from future medical advances), scientific spillover (benefits beyond the original innovation), etc.[19] The challenges raised in assessing the value of NGS-based testing are broad, which lead to uncertainty concerning which evidence (endpoints, appropriate and novel trial designs, real-world evidence and emerging applications evolving over time) needs to be made available for patients to be able to access multigene NGS testing and benefit from the interdependent technologies to achieve better outcomes.

> From a precision public health perspective, the focus is on using data to improve health and achieve social justice–equity, social inclusion, and empowerment.

Value frameworks provide guidance for evaluating the value of NGS testing, but the current reality is that similar evidence leads to divergent decisions. In the United States, the most recent data from the Centers for Medicare & Medicaid Services (CMS) on Medicare payments show that a sizeable fraction of prescribed NGS testing for Medicare patients is denied reimbursement and that denial rates vary significantly among the payers managing these benefits in their designated regions of the country.[2] Decisions on which NGS testing is covered also vary by Medicare payers, contributing to differences in reimbursement and access to such testing across the United States.[20]

Variability in non-Medicare reimbursement coverage decisions among the multiple national and regional payers also contributes to delays in, or complete barriers to, patient access to NGS testing and potentially to best-informed treatment.[21-24] Examples of NGS tests with coverage policies that are divergent across large national and regional payers—despite citing very similar evidence sources in their decision making—include whole exome sequencing in neurodevelopmental disorders, and multigene liquid biopsy testing in oncology (payers reviewed by the authors included Aetna, Anthem BlueCross BlueShield of California, BlueCross BlueShield of North Carolina, Cigna, Humana, and United Healthcare 2020).

A similar situation of divergent NGS test access decisions can be observed across the globe.

Additional uncertainty for prescribers, providers, and developers of NGS-based tests derives from:

- Incentives and priorities of multiple stakeholders
- Nontransparent decision-making criteria/different approaches to valuation
- Limited consideration of unique components of value associated with simultaneously testing multiple analytes
- Nonvalue-based payment with little or no intellectual property protection and high utilization management
- Demand for infeasible drug trial-type study designs

The current access situation calls for the collaboration of all NGS testing stakeholders to create a common ecosystem value of solutions in the context of precision medicine, covering value criteria used for deciding access/adoption, stakeholders to whom the integrated ecosystem value can be proven, and funding/coverage to provide access to clinically useful NGS testing.

Conclusion

There is a need for the current value framework approach for NGS testing access decision making to evolve to a more transparent and harmonized evidence-based approach with clear value criteria addressing the perspectives of multidisciplinary stakeholders covering the entire healthcare ecosystem. This would enable an integrated value-based pathway forward for all stakeholders, most importantly patients, to be able to benefit from these healthcare innovations.

To further clarify the current situation and propose solutions for global NGS testing stakeholders to improve value assessment, 2 ISPOR Special Interest Groups (SIGs)—the Medical Devices and Diagnostics SIG and the Precision Medicine and Advanced Therapies SIG—announced a recently approved joint SIG special project to advance the transparency and evidence basis upon which multigene NGS tests and NGT approaches overall are evaluated and access decisions are made. This work will involve a detailed analysis and consideration of the value assessment landscape along with recommendations aimed at addressing the unique characteristics of NGT as an important innovation towards personalized medicine.

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Predicting the Impact of Vaccination Strategies in the COVID-19 Pandemic Using a Susceptible-Exposed-Infectious-Removed Model

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The authors developed a SEIR model to predict the impact of different COVID-19 vaccination strategies.

Vaccinating the 65+ age group first resulted in the lowest costs in both critical and noncritical care.

Findings from this study can help to inform government policies regarding the delivery of vaccines to ensure efficient use of the limited resources available.

Background

The COVID-19 pandemic has resulted in 180 million infections and 3.9 million deaths worldwide and both figures are still rising.[1] Variants of the virus are threatening to produce new waves of infections with no sign of extinction at the present time.[2] The consequences of the pandemic, both direct and indirect, on healthcare systems, social life, and economic activities are unprecedented.[3]

Despite policy measures such as social distancing or lockdowns and improvement in diagnosis and treatment of COVID-19, it has become apparent that vaccines provide the best protection against the spread of the disease.[4] A range of vaccines have been approved already and are being administered within several countries. However, supply of safe and effective vaccines will be limited in the foreseeable future by production and distribution capacities. Therefore, a vaccination strategy must be based on the prioritization of specific population subgroups to minimize the disease burden.

Our Approach

We developed a susceptible-exposed-infectious-removed (SEIR) model in R Project® to predict the impact of different COVID-19 vaccination strategies on the number of infections, mortality, healthcare burden, and productivity loss in the United Kingdom.[5]

Given the uncertainty in vaccine supply, 3 scenarios were explored where 20%, 50%, and 70% of the United Kingdom population were vaccinated. For each of the 3 scenarios, 3 population-wide vaccination strategies with different age group priorities (0-14, 15-34, 35-64, ≥65) were modeled in addition to no vaccination. For each vaccination strategy the total number of infections, COVID-19 related deaths, quality-adjusted life years (QALYs) loss, hospitalization costs, and productivity loss were estimated (**Table**).

Age-group specific proportions of asymptomatic infections, probability of severe symptoms, and death rates were identified from published literature. Key parameters defining individuals moving through the model include rate of infection, rate of removal, and basic reproduction number. QALY losses were estimated through the standard life table approach with quality adjustment[6] and time preference discounting.

> The issue of vaccination is a complex one, and the limitations of this research must also be acknowledged so that the evidence can be applied appropriately to decision making.

Hospitalization costs included critical and noncritical care for symptomatic patients based on different inputs on service utilization and length of stay. National Health Service reference costs were used to calculate the hospital costs per day.[7] Productivity loss measured as working days lost was calculated for the working-age population based on weighting the number of days spent in hospital care and the number of days being mildly symptomatic due to an active COVID-19 infection.

Results

As shown in the **Table**, under each vaccine supply scenario, the model predicted that vaccinating the 15–34 age group first would lead to the lowest number of infections as well as the lowest loss of QALYs, while vaccinating the 65+ age group first would result in the lowest number of deaths. When considering the impact on healthcare resource use, vaccinating the 65+ age group first resulted in the lowest costs in both critical

and noncritical care, as well as total hospitalization costs, compared to other vaccination strategies. The model further showed that vaccinating the 15–34 age group first was the most effective strategy for minimizing productivity loss, followed by vaccinating all age groups proportionally.

All vaccination strategies performed better over no vaccination for all the outcomes measured. For each outcome, the patterns observed with the order of priority for different population subgroups did not change when the vaccine supply increased from covering 20% to 50% and 70% of the population, respectively. All outcomes improved with greater vaccination coverage, although the differences in each outcome across the vaccination strategies for vaccinating different age groups first were smaller, suggesting prioritizing age groups is more important when supply or coverage is low.

Implications for the Future

COVID-19 has severely impacted all sectors of society across the globe. Vaccinations play a vital role in curbing the effects of the pandemic, but the availability of safe and effective vaccines at any one point in time is limited. National, regional, and global decision makers need to establish strategies on procuring, paying for, distributing, and using new vaccines against COVID-19.[8,9] Giving priority to the appropriate subpopulation at each stage is essential to maximize the health, social, and economic benefits of immunization.

Compartmental models such as SEIR can be useful to support informed decisions on various vaccine strategies for COVID-19.[9] Parsimonious compartmental models have been widely applied in the field of infectious disease, as they require a small number of predictor variables to generate significant explanatory power. This is advantageous especially during the earlier phases of the pandemic, where decisions need to be made with constraints on available data. The simplicity and easy maintenance of the SEIR model means that it is an ideal tool for prompt analysis and continuous update of the potential effects of interventions. This study explored its application in health economic evaluations of COVID-19 vaccination strategies in the United Kingdom.

Our findings confirmed that all vaccination strategies produce desirable reductions in numbers of

Table. Vaccination strategies and predicted outcomes.

Vaccination strategies		Health outcomes			Hospitalization costs (£1 million)			Productivity loss (1,000 person-day)
		Number of infections (1000)	Number of deaths (1000)	QALY loss from death	Non-critical care	Critical care	Total hospitalization	
No vaccination (Base case)		63,712	2669	31,222	£63,730	£71,197	£136,262	356,182
20% initial vaccine availability	Vaccine prioritization of the elderly age group (≥65)	53,905	1779	25,440	£47,047	£52,559	£100,495	330,767
	Vaccine prioritization of the young age group (15-34)	50,910	2390	24,758	£53,654	£59,940	£114,789	248,652
	Vaccination coverage spread proportionally across age groups	52,848	2280	26,159	£53,920	£60,238	£115,298	293,749
50% initial vaccine availability	Vaccine prioritization of the elderly age group (≥65)	38,918	1450	19,223	£36,815	£41,129	£78,669	238,120
	Vaccine prioritization of the young age group (15-34)	35,102	1797	17,463	£39,161	£43,750	£83,810	162,763
	Vaccination coverage spread proportionally across age groups	36,553	1696	18,565	£39,206	£43,799	£83,852	200,098
70% vaccine availability	Vaccine prioritization of the elderly age group (≥65)	27,375	1165	14,018	£28,161	£31,461	£60,205	162,232
	Vaccine prioritization of the young age group (15-34)	25,047	1376	12,944	£29,587	£33,053	£63,329	116,320
	Vaccination coverage spread proportionally across age groups	25,690	1306	13,502	£29,396	£32,840	£62,888	137,664

infections, mortality, QALY loss, and productivity loss compared to no vaccination. Furthermore, while the optimal vaccination strategy will differ depending on what objectives are desirable, prioritization of specific population subgroups is shown to be key for achieving these outcomes. In contrast, a strategy where all age groups are vaccinated simultaneously in a proportional fashion leads to the heaviest burden on the health system as well as the highest costs. These findings are consistent with published studies in the United Kingdom,[13] and in line with the advice provided by the UK Joint Committee on Vaccination and Immunization,[14] which suggests prioritizing the direct prevention of mortality, as well as supporting the National Health Service and social care systems. These findings may be useful for countries that are still developing the vaccination programs for COVID-19.

The issue of vaccination is a complex one, and the limitations of this research must also be acknowledged so that the evidence can be applied appropriately to decision making. The model focused only on vaccine distribution across different age groups and no other health conditions were incorporated. It also did not consider different types of vaccines and nonpharmacological interventions, nor did it consider virus mutations that are resistant to current vaccines and the possible implications for long-term immunity achieved with vaccination. The model assumed immediate immunity following vaccination without considering different vaccine timing and lengthy booster shot cycles required by different vaccines. Revised models incorporating more relevant factors are an area for further research.

When ranking the strategies, the outcome domains for each strategy were considered separately. However, in reality, vaccination strategies need to account for multiple outcomes simultaneously. This can be achieved through cost-effectiveness analysis to encompass wider costs and benefits within society or multicriteria decision analysis where several relevant criteria can be considered and weighted explicitly, leading to more informed decisions with a broader perspective of the issue.

Closing Thoughts

In conclusion, vaccines are important healthcare interventions for fighting COVID-19. A SEIR-based model requires little data to predict clinical and economic outcomes of alternative vaccination strategies and is easily adaptable in fast moving situations. SEIR can be a useful tool to inform decisions on vaccination strategies including the selection of different types of vaccines for different population. However, policy makers are required to establish clear goals and objectives with predefined criteria for measurement before the optimal strategy can be identified. Supported with more accurate data, findings from this and similar modeling studies can help to inform government policies regarding the procurement and delivery of vaccines to ensure efficient use of the limited resources available. Although this study focused primarily on the United Kingdom, the results serve as a framework that can be applied to any country when devising COVID-19 vaccination strategies as well as other forms of interventions for tackling future pandemics.

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When Increasing Severity of Parkinson's Disease Leads to Increasing Costs: Results From Register-Based Research in a Swedish Setting

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The authors find that Parkinson's disease is associated with large direct and societal costs, which increase considerably as the disease progresses.

Few cost-of-illness studies have investigated the economic burden of Parkinson's disease by level of severity.

Physician- and patient-reported data on severity level from a patient register was linked to administrative data on all filled prescriptions and all healthcare visits to primary care and specialized outpatient and inpatient care.

Parkinson's Disease in the Aging Population

Parkinson's disease is a chronic and progressive neurologic disease that has no cure. With an aging population, the prevalence of Parkinson's disease is growing, and over the past generation the global burden of Parkinson's disease has more than doubled.[1] Parkinson's disease is associated with large societal costs[2,3] and the disease has a major impact on the health-related quality of life (HRQoL),[4] which deteriorates as the disease progresses. The disease is characterized by motor symptoms including shaking, stiffness, and difficulty with walking, balance, and coordination, but also nonmotor symptoms including drooling, constipation, low blood pressure when standing up, voice problems, depression, anxiety, sleep problems, hallucinations, and dementia. In severe stages, people with Parkinson's disease may have difficulties taking care of themselves and then they require extensive use of formal care such as home help, home healthcare, institutional care, and informal care, that is, unpaid care performed by family and friends.

> With an aging population, the prevalence of Parkinson's disease is growing and over the past generation, the global burden of Parkinson's disease has more than doubled.

Few cost-of-illness studies have previously investigated the economic burden of Parkinson's disease by level of severity of the disease, especially while applying a societal perspective including both direct and indirect costs. In a recently published study[5] we analyzed cost and resource use in Parkinson's disease by severity measured by the Hoehn and Yahr scale, which is a commonly used classification of Parkinson's disease progression including 5 health states ranging from (1) "Unilateral involvement only usually with minimal or no functional disability" to (5) "Wheelchair bound or bedridden unless aided." Costs were also presented by percentage of awake time in "off" ("off-time"), which refers to periods of the day when there is poor response to levodopa treatment, causing worsening of Parkinson's disease symptoms. These severity levels are in line with current health economic modeling practice of interventions in Parkinson's disease, for which Hoehn & Yahr and "off-time" are the most used health states.

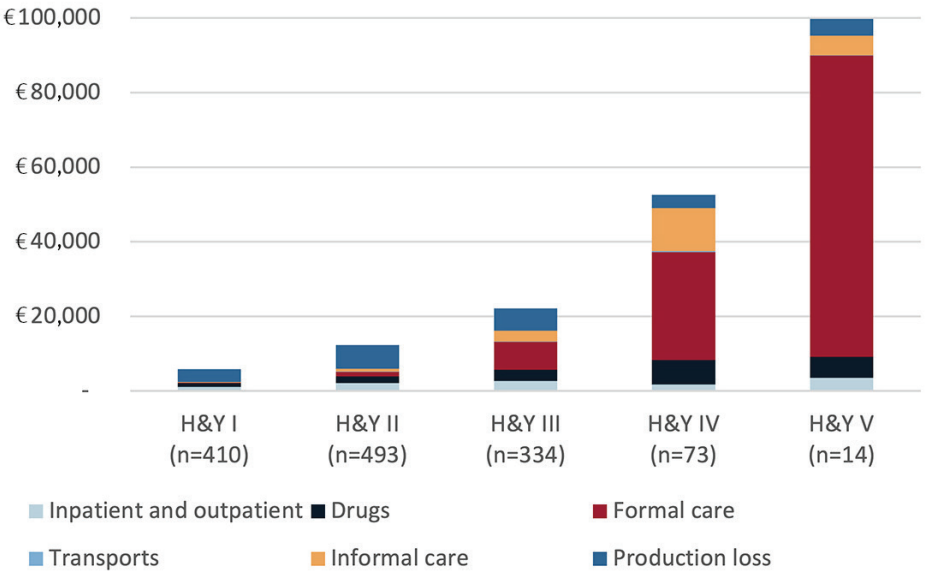
Unique Swedish Data

The study was based on the Swedish Parkinson's disease patient registry, PARKreg. PARKreg has been developed by the Swedish Movement Disorder Society in cooperation with Swedish Neuro Registries since 2012 and includes information on diagnosis, treatments, and outcomes in terms of clinical data and patients' HRQoL. PARKreg presently includes information on 8200 patients with Parkinson's disease. The register provides a unique opportunity to analyze real-world data in Swedish clinical practice since observations in PARKreg reflect clinical practice (ie, they occur when patients visit their neurologist and are not protocol driven).

Sweden has a system of unique personal identification numbers that makes it possible to link so-called quality registers, such as PARKreg, to other registries with individual-level administrative data. This creates a unique combination of patient-reported data of HRQoL, physician-reported data of clinical severity, and almost complete administrative data regarding resource use, costs, treatment patterns, and comorbidities.

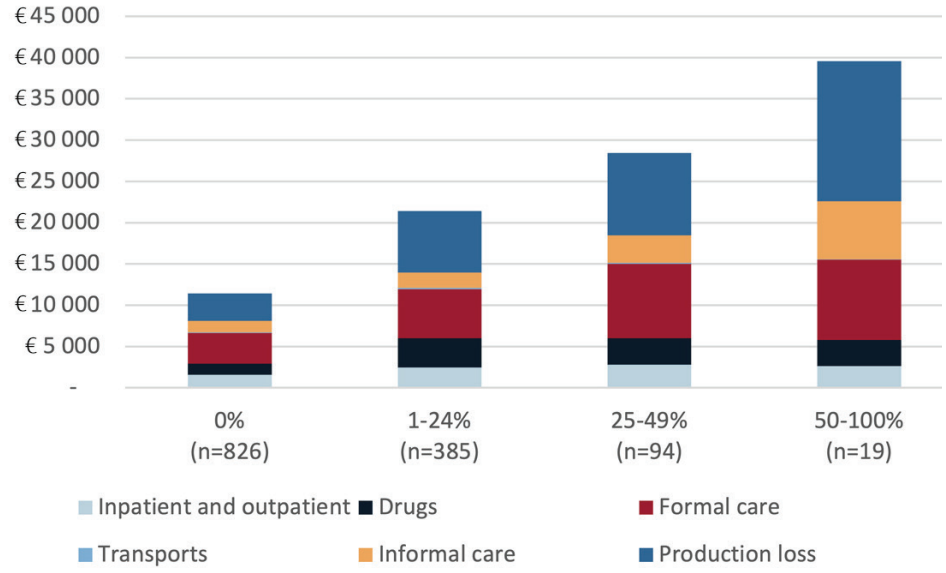
In our study, we included patients in PARKreg with idiopathic Parkinson's disease in the Region of Skåne, a relatively large region in southern Sweden, comprising approximately 13% of the total Swedish population. The data were linked to the national prescribed drugs register, which contains close to 100%

Figure 1. Total mean costs in € 2019 per year according to Hoehn and Yahr stage.



H&Y indicates Hoehn and Yahr.

Figure 2. Total mean costs in € 2019 per year according to "off-time."



of all filled prescriptions, and the Skåne Healthcare Register, which contains all healthcare visits to primary care and specialized outpatient and inpatient care.

Patient-reported data on formal care, informal care, transportation, and sick leave were collected from PARKreg. Data on formal care included information on whether the patient stayed at a nursing home, estimates of hours per week with home help or personal assistance, number of visits with home healthcare, and use of an electric wheelchair or electric scooter during the last year.

Data on informal care included number of hours per week that a family member had abstained from work or from leisure time to care for their relative. Information on transportation included the number, type, and length of transportation to healthcare visits during the last year. Patient-reported data on long-term sick leave and early retirement were also collected.

Healthcare contacts included all contacts to primary care, specialized outpatient care, and inpatient care registered with diagnosis codes for Parkinson's disease. Contacts included visits, inpatient stays, letters, and phone calls as provided by all types of professions such as physicians, nurses, and physiotherapists. All filled prescriptions of antiparkinsonian drugs were included.

Parkinson's Disease and Costs

The overall objective of the study was to estimate resource use and costs, including both direct and indirect costs in relation to levels of disease severity as measured by the Hoehn and Yahr scale and in relation to the periods of the day with poor response to the levodopa treatment (ie, the off-time).

The sample included 1324 observations. The majority (68%) of the observations were reported with Hoehn and Yahr scale stages I and II, 25% with stage III, 6% with stage IV, and 1% with stage V.

This study showed that the more advanced and late stages of Parkinson's disease are associated with significant societal costs, and a large proportion are costs for formal care. Total mean cost per patient-year was estimated to approximately €16,000 and ranged from about €6000 for Hoehn and Yahr I to €100,000 in Hoehn and Yahr V, as illustrated in **Figure 1**. In the early stages of the disease, the dominating part of total costs were indirect costs; accounting for between 50% and 60%. For the more advanced and late stages of the disease, the dominating parts of the costs were formal care, accounting for between 30% and 80% of total costs. The study also demonstrated that total mean costs increased with increasing off-time (**Figure 2**).

The Problem of Budget Silos

As our study shows, Parkinson's disease is an illustrative example of a disease associated with aging where a large part of the costs is borne by the municipalities. Because healthcare in Sweden is provided by the regions, these different cost-bearing silos may cause poor economic incentives to provide cost-effective care for this patient population. For example, device-aided therapies for Parkinson's disease, which include deep brain stimulation (surgical insertion of treatment electrodes in the brain) and pump-based continuous delivery of levodopa-carbidopa intestinal gel, levodopa-entacapone-carbidopa

intestinal gel, or apomorphine to avoid motor fluctuations and dyskinesias (unwanted movement), have shown to be difficult to implement in clinical practice even though they are considered cost-effective therapies.[7] This could be caused partly by the fact that the relatively high costs of providing device-aided therapies are borne by the regions, whereas the benefits, in terms of large cost offsets due to reduced need for home help and nursing homes, are captured mainly by the municipalities. The problem is that budget silos (which has been discussed elsewhere[8-10]) will become increasingly challenging with an aging population and with an increased prevalence of aging diseases such as Parkinson's disease.

> Parkinson's disease is an illustrative example of a disease associated with aging where a large part of the costs is borne by the municipalities.

Closing Thoughts

In conclusion, our study shows that Parkinson's disease is associated with significant societal costs, which increase considerably as patients in advanced and late stages often require resource-intensive and costly formal care. Consequently, substantial cost savings can potentially be made by optimizing the healthcare of patients in advanced and late stages, and by putative future disease-modifying therapies.

As future putative disease-modifying therapies become available for people with Parkinson's disease, the industry, healthcare providers, and payers need to overcome challenges including budget silos and affordability to ensure sustainable and timely access to these therapies.

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Editor's Note: In this issue of Value & Outcomes Spotlight *we feature a new column wherein readers respond to a previously published article. This article was written in response to a piece published in the May/June issue, "Fit-for-Purpose Real-World Data Assessments in Oncology: A Call for Cross-Stakeholder Collaboration," by Desai, et al.*


HEOR ARTICLES

Fit-for-Purpose Real-World Data Assessments in Oncology: A Call for Cross-Stakeholder Collaboration

Taking the Call: Multisource Datasets Speed Real-World Data Fitness Assessments in Oncology

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An article published by Desai, et al[1] that appeared in the May/June 2021 issue of *Values & Outcomes Spotlight* defined the promise and challenges associated with using real-world evidence (RWE) that draws on real-world data (RWD) sources for health economics and outcomes research (HEOR).

In agreement with Desai, et al, there remains a need for clearly outlined "use-case specifications," broadly defined as specifications of RWD requirements and criteria to evaluate RWD fitness for use for specific RWE use cases. Given this, it is undeniable that, per the authors, a relevance assessment framework will drive benefits for all stakeholders involved in the use-case specification development and maintenance effort. Certainly, as they've written, a cross-stakeholder collaboration is required to arrive at a shared definition of use-case specifications, including relevant quality thresholds and identification of benchmarking resources for validation strategies.

The Use-case specific Relevance and Quality Assessment (UReQA) put forth by Desai, et al is an excellent, accurate framework. Yet, to further streamline assessment and use of RWD by researchers, a preceding broader examination of a database's makeup and ability to support a spectrum of oncology research needs is proposed. As Desai, et al state, there are many real-world databases and it is a challenge to determine which are appropriate. Those that incorporate a multisource data strategy are more likely to overcome limitations often inherent in individual data sources. In addition to the uses listed by Desai, et al, when a broader dataset is applied, RWD have the potential to support an expansive ecosystem of partners with patient identification for clinical trials, health disparities and outcomes research, tailoring optimal treatment regimens, understanding distinct populations, handoffs from nononcology and oncology providers, and developing more cost-efficient external control arms. The ability to leverage one rich dataset to answer multiple questions promotes efficiency and therefore time and cost savings.

Understanding the Inherent Strengths and Limitations of Individual RWD Sources Before the Use Case

As outlined by Desai, et al, regulatory and payer guidelines have highlighted "fitness for use," also known as "fitness for purpose," as a key factor that drives the choice of RWD and analytic methods for RWE generation. In determining fitness for use, questions about a particular RWD source can range from quantitative in nature (eg, patient counts and percent missingness) to qualitative (eg, data quality and population similarity). Building upon the UReQA framework, to streamline determination of fitness for use of a particular use case, we propose the need for a qualitative and quantitative deep dive into distinct RWD sources' data quality even prior to determining specific use cases.

Both dimensions of data quality (reliability and relevance) may be applied to RWD source evaluation prior to the specific use case, instead taking into account the broad array of oncology research questions first—from care prior to cancer diagnosis to outcomes. In determining reliability, completeness, accuracy, and consistency are evaluated; while relevance is thought of in terms of recency, representation, and historical capture. No single data source passes all quality dimensions. For example, hospital tumor registries are highly regarded and very reliable, but the existence of certain elements (eg, recurrence, biomarkers, safety events) critical for select research questions might be absent depending on the individual registry and as such they too are limited in longitudinally and comprehensiveness. Claims data may lack key patient characteristics and presentations relevant for study questions. Data sources originating from the outpatient care setting lack the full scope of care that take place within the inpatient hospital setting. Because all RWD sources have their limitations,

one RWD source is less likely to meet fit for purpose parameters on its own. Researchers should evaluate the specific strengths and limitations of individual data sources to determine appropriate research questions and use cases that can be addressed and then, what other data might be needed. The analogy of Swiss cheese is helpful here: every source has gaps throughout, just as every slice of Swiss cheese has holes throughout. But if you place enough slices of Swiss cheese on top of each other, you're likely to fill in all the gaps.

A Multisource RWD Strategy to Promote Sustainability and Efficiency

Once we have a clear picture of each individual RWD source, we can begin to build a multisource RWD strategy that brings disparate, overlapping data sources together into a single comprehensive view of the patient journey that can be used to inform a variety of research needs.

The ability to leverage one dataset to answer multiple questions promotes efficiency and therefore time and cost savings. In this way, the suitability and sustainability of a particular dataset for a partner organization may lie in its ability to meet that organization's diverse research needs. However, diverse research needs compound the existing challenges to working with heterogeneous RWD. It should be noted that gathering multiple large datasets onto a single platform is not the same as linking and integrating information data into a single patient record, which may require collaboration with health systems with multiple electronic medical records, sourcing from different systems internally, as well as laboratories at varying levels of sophistication and wide diversity and reporting standards. Layering multiple sources together is a more complex, challenging undertaking than relying on a single RWD source for insights, but it enables us to develop a much more complete picture of each patients' cancer care journey.

For these reasons, we propose furthering the UReQA framework with additional metrics for the assessment of RWD fitness for use—particularly under pre-assessment, whether multiple data sources are employed. Under relevance, in addition to representation, it is pertinent to ask whether there is a comprehensive list of data elements (exposures, outcomes, covariates), whether there is longitudinally to reflect the full course of care and patient response, and are the data recent to adequately reflect actual outcomes?

While not generated for the purpose of research use, if appropriately handled and analyzed, RWD can unlock immense value. At a high level, RWD support diverse research needs across the healthcare continuum, including by:

- Helping to clarify how therapies perform in real-world populations that are underrepresented in clinical trials (eg, in minority communities patients with comorbidities and the aging population).
- Helping providers identify and close gaps in care to ensure every patient is given their best shot at managing their disease effectively.

Every dataset certainly has a limitation but with collaboration there is a way to fully realize the potential of RWD. In doing so, not only data quality but also methodological and analytical robustness must be considered to unlock the potential of RWD. Underlying the potential success of all these efforts is transparency and ongoing discussion and collaboration at an industry level to move the field forward.

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Are Smartwatches Good for Your Health?

A Conversation With Rodrigo Mello Ferreira, MD

Photo courtesy of Rodrigo Mello Ferreira

Q&A

Section Editor: Marisa Santos, PhD, MD, Instituto Nacional de Cardiologia, Rio de Janeiro, Brazil

I spoke with Rodrigo Mello Ferreira, MD, Professor, D'Or Institute for Research and Education Board Member, Centro Médico Pastore, Rio de Janeiro, Brazil, who works in the field of bariatric and metabolic surgery, and is a smartwatch researcher. He looks at the current implications in the aging population and thinks the applications of this technology will only grow with time.

"The elderly patient will be the biggest beneficiary from the use of these devices. When compared to other devices, measuring blood pressure through a wearable is easier and more practical."

Value & Outcomes Spotlight: A new generation of wearable devices has been developed that focuses on individual health. Is there a real benefit here or are these just marketing gimmicks to increase sales?

Rodrigo Mello Ferreira: Yes, there are benefits. The research aims precisely at the scientific validation of the technology used in wearables to assess oximetry and blood pressure. We are evaluating the effectiveness of these technologies. However, even without this validation, just encouraging healthcare and monitoring would be a benefit.

VOS: What are the benefits of smartwatches for senior citizens?

RMF: The elderly patient will be the biggest beneficiary from the use of these devices. When compared to other devices, measuring blood pressure through a wearable is easier and more practical. In addition, there are many possibilities, such as continuous monitoring, fall assessment, and medication alerts, among others—all this using a device that is much more practical and familiar in our routines.

VOS: Have you worked with athletes that wear smartwatches? Is there anything they can do to help?

RMF: I've haven't worked with athletes yet. But the use of smartwatches and other wearables is already a reality in the daily lives of high-performance athletes, whether in injury prevention or in monitoring results.

VOS: How committed are users to smartwatch monitoring and what are the barriers to broader adoption?

RMF: In my opinion, the high cost of some of these devices is the biggest barrier. Other reasons are the acceptance of health professionals and the validation of the technology. The users' commitment should be minimal. The artificial intelligence will do all the work, they just need to use the wearables.

VOS: How accurate and reliable is the smartwatch monitoring?

RMF: This is the main focus of the current research: technology validation for further specific analysis.

VOS: Have you used smartwatches for patients with heart failure before?

RMF: No, I haven't. After technology validation and the development of software, hardware, and application, we will try to prove the effectiveness of these devices, including in heart failure.

VOS: What can we expect in the next 10 years from this technology?

RMF: It is unlimited. The most important thing is to expand access by lowering the cost. In my view, at minimum, we can expect continuous monitoring and diagnosis of high blood pressure, with home and outpatient blood pressure monitoring, not to mention services related to geolocation.

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