SEPTEMBER/OCTOBER 2019 VOL. 5, NO. 5

VALUE & OUTCOMES SPOTLIGHT

An ISPOR publication for the global HEOR community

Aging of the Global Population

ALSO:

All data are not created equal. Understanding and predicting outcomes and costs requires specialized data.

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VALUE & OUTCOMES
SPOTLIGHT

SEPTEMBER/OCTOBER 2019
VOL. 5, 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.

ISPOR
Improving healthcare decisions

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FROM THE EDITOR

A common refrain is that "getting old sucks, but it beats the alternative." Strictly speaking, those of us in the HEOR community know this to be not quite true, as there is the possibility for certain living health states to have negative utilities, meaning they are in fact worse than death and its utility of zero.

Healthcare is all about increasing the length and quality of life—in other words, making the process of getting old a little bit longer and a little less … well, *sucky*. On a macro level, innovations in medicine and advances in healthcare provision have certainly contributed to increased life expectancies, but whether or not these have improved comfort and well-being among the elderly remains a subject of hotly contested debate. (Don't *EVEN* get my Mom going on this issue!)

Aging presents a whole host of additional challenges to health systems when examined at the population level. This is the theme of this issue of *Value & Outcomes Spotlight.* Our feature article highlights some of these challenges, including changes in case-mix faced by healthcare providers (tilting towards conditions primarily affecting the elderly, such as dementia), shifts in settings/ mechanisms for care delivery (increasing demand for home healthcare workers), and difficulties in healthcare financing (arising from a shrinking working-age population having to fund care for a growing population of retirees). We also include thought pieces on this issue from various parts of the world, including Asia and Latin America. We have a by-the-numbers infographic and, to cap things off, our Q&A section features long-time ISPOR contributor Isao Kamae PhD, MD, of the University of Tokyo in Japan, a country with demographic trends that are particularly daunting.

In addition to the population-aging themed content, we include a variety of material that is relevant to our Society. We have 3 HEOR articles on the topics of drug disinvestment, European HTA submissions, and data quality in real-world evidence generation. Our ISPOR Central section features a profile of Marc Berger MD, who we congratulate for this year's Avedis Donabedian Lifetime Achievement award, ISPOR's highest honor. Finally, we include background materials for upcoming ISPOR conferences, including the ISPOR Europe 2019 meeting, which will take place in Copenhagen this November.

See you in there!

David Thompson, PhD
Editor-in-Chief,
Value & Outcomes Spotlight

ISPOR SPEAKS

ISPOR Conferences: Bringing Us Together to Advance HEOR Around the World

Julie McGrath, Senior Director, ISPOR Global Events

People have long gathered together to share knowledge and to introduce buyers to sellers. The first "fairs" (as they were called) can be traced back to the European Middle Ages, and history shows early examples of these gatherings at the Egyptian, Greek, and Roman marketplaces.[1] The first scientific meetings were traced back to 1640 London where men (and yes, at that time it was just men) who were interested in discussing science began to meet regularly. In the United States, one of the first large meetings took place in 1848, as a group of scientists met in Philadelphia for 6 days of discussion and to establish the American Association for the Advancement of Science.[2]

ISPOR was founded with the goal of serving as a catalyst for advancing the science and practice of health economics and outcomes research (HEOR) around the world. In keeping with its mission, ISPOR launched its first conference in 1996 in Philadelphia, PA, with 382 attendees. Over the years, ISPOR's conferences have grown and expanded, reflecting the global growth in the importance of HEOR and the evolving needs of our members.

For nearly 25 years, the *ISPOR Annual Conference* (which will be held in Orlando, Florida in May 2020) has been the Society's flagship event. Held each year in North America, this conference brings together a diverse group of nearly 4000 global leaders in HEOR and from all sectors of healthcare.

ISPOR Europe was launched in 1998 in Cologne, Germany to address the growing needs of our European members for HEOR information and education. Held annually in rotating countries, the conference attracts more than 5000 attendees and is considered the leading European conference for HEOR. The city of Copenhagen will host the 2019 event and then ISPOR is off to Milan in 2020.

As ISPOR's global footprint continued to grow, new regional chapters developed in the Latin America and Asia Pacific regions. As membership and engagement in these regions grew, so too did the need for HEOR education and training programs that were specific to the populations in these regions. This mission-related need resulted in the development of 2 additional Society conferences (held in alternate years) in Asia and in Latin America.

The goal of these conferences is to bring together experts representing diverse perspectives to share innovative research and health policy developments, and ultimately, to provide an opportunity to learn from each other to advance the science of HEOR.

ISPOR Latin America was launched in 2007 in Cartagena, Bogotá. The biennial regional conference attracts approximately 1000 attendees. Although many of the participants come from around the world, the majority of attendees are regional, and the education is focused on exploring the key issues for healthcare in Latin America. The conference came full circle in September of this year when we returned to Bogotá. Mexico City is preparing to host this conference in 2021.

ISPOR Asia Pacific was launched in 2003, and by 2008 nearly 1000 attendees convened in Seoul, South Korea for the third in ISPOR's biennial regional conference series. The conference will head back to Seoul again in 2020, with an education program focused on HEOR and issues in healthcare affecting and influencing the Asia Pacific region.

In addition to these 4 core conferences, ISPOR also convenes smaller events that have either a specific regional focus (eg, Warsaw, Poland; Dubai, United Arab Emirates, etc), or a topically focused discussion, like our ISPOR Summits, that concentrate on single topic issues in the field of HEOR (eg, value assessment frameworks, real-world evidence, etc).

In summary, ISPOR conferences provide a forum for discussion and dissemination of information surrounding the science of HEOR. The goal of these conferences is to bring together experts representing diverse perspectives to share innovative research and health policy developments, and ultimately, to provide an opportunity to learn from each other to advance the science of HEOR. In addition to the scientific and educational content, the conferences provide a platform for our members to advance their professional careers through publishing, presenting, networking, and leadership development opportunities.

We have certainly grown and expanded since that first Annual Conference almost >

25 years ago. And we will continue to enhance our conferences to reflect the growth in HEOR and to respond to the evolving needs of our members. Over the past few conferences, we have been upgrading our use of technology and adding new program features, such as our Spotlight sessions, new Short Course topics, and the addition of more advanced content. Look for further enhancements to our content and program at our upcoming conferences.

We encourage you to attend an upcoming ISPOR event...and if you have recently attended one of our conferences, we welcome your feedback too — conference evaluations help guide our direction for future events. Until then, I look forward to greeting you at a future ISPOR conference!

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1. Marrow SL. *The Exhibition Industry: The Power of Commerce.* Cherbo Publishing Group; December 2003.

2. Egger AE, Carpi A. The How and Why of Scientific Meetings. http://www.Visionlearning.com/en/library. Accessed September 16, 2019.

HEOR NEWS

A diverse collection of news briefs from the global HEOR community.

1 Forging a New Path to Commercialization for Cell and Gene Therapies (Deloitte)

Deloitte's Greg Reh summarizes the panel discussion from the *Financial Times* US Pharma and Biotech Summit about the changes needed to face coming innovations in manufacturing, pricing, and reimbursement of personalized therapies. According to the panelists, these innovations include direct-to-payer models, mass customization, and valuation of gene therapies and one-time treatments.

https://tinyurl.com/y42rqxhd

2 ICER Publishes Evidence Report on Treatments for Duchenne Muscular Dystrophy (ICER)

In its most recent report looking at treatments for Duchenne muscular dystrophy, the Institute for Clinical and Economic Review (ICER) concludes that the price for the corticosteroid deflazacort would require a 73% to 83% discount off the treatment's wholesale acquisition cost to be cost-effective.

https://tinyurl.com/yyf5ekmc

3 Value Our Health: Stop Discriminatory Value Assessments (Morning Consult)

Elizabeth Franklin, executive director of the Cancer Policy Institute at the Cancer Support Community headquarters in Washington DC, makes an argument on the Morning Consult blog that the United States should eliminate "discriminatory measures" such as the quality adjusted life year, or QALY, for assessing the value of therapies for those with chronic conditions and disabilities.

https://tinyurl.com/y5r52477

4 Using All-Payer Data to Conduct Cross-State Comparisons of Health Insurance Enrollment (Health Affairs Blog)

A recent study at the Health Affairs blog showed how all-payer claims databases (APCDs) can be used to show how Americans move through the health insurance system. The study, which looked at combined APCDs from neighboring Utah and Colorado, used the combined data sets to estimate transition rates between Medicaid and Marketplace coverage in Colorado and evaluated the effect of Colorado's Medicaid expansion on continuity of Medicaid enrollment with Utah as the comparator.

https://tinyurl.com/y35r95hn

5 Novartis Struggling to Win Payer Coverage for $2.1M Gene Therapy Zolgensma: Analysts (FiercePharma)

Novartis is having difficulties getting payers to cover the $2.1 million price tag for its spinal muscular atrophy drug Zolgensma. Even though only about one-third of the top 30 US insurance companies have made their decisions about how to cover the drug, analysts at Bernstein are worried.

https://tinyurl.com/yxq26ul4

6 The FDA's Janet Woodcock Talks About Some Big Changes She's Pushing for in Drug Development, and Agency Reviews *(Endpoints News)*

Janet Woodcock, chief of the FDA's Center for Drug Evaluation and Research, recently discussed a host of key changes being made at the agency in clinical trial design, covering aspects such as support of noninferiority and other trial protocols, including dose comparisons and delayed start trials; a coming guidance on trial design around patient-focused clinical design work; and how to evaluate new drug/device combinations.

https://tinyurl.com/y4hfnf5a

7 A Probe Into the Wages and Salaries of Health Economics, Outcomes Research, and Market Access Professionals (Applied Health Economics and Health Policy)

In a paper in the journal *Applied Health Economics and Health Policy*, Manuel J. Carvajal, Patti Peeples, and Ioana Popovici found that men earned higher wages and salaries than women, and within each gender, health economics/outcomes research/market access (HE/OR/MA) professionals living in the United States earned higher wages and salaries than those living outside the United States.

https://tinyurl.com/yxlysk4f

8 Trump Plans Drug Pricing Executive Order Aimed at Ensuring that the US Pays Less Than Other Nations (STAT)

President Trump says his administration would soon issue an executive order mandating a "favored nations" policy in which US payments for drugs are capped at the lowest price paid by either a manufacturer or a developed country.

https://tinyurl.com/yxtfahjv

9 On What We Have Learned and Still Need to Learn About the Psychosocial Impacts of Genetic Testing *(The Hastings Center Report)*

The Hastings Report has published a collection of essays from a conference to answer questions about the ethical, legal, and social concerns regarding the negative psychosocial impacts of genetic testing and to consider whether future research might benefit from different methods than have been used to date.

https://tinyurl.com/y5cdwjog

CONFERENCES & EDUCATION

ISPOR Summit 2019

ISPOR'S Real-World Evidence Transparency Initiative

October 11 | 8:00 am – 4:00 pm

Baltimore Marriott Inner Harbor at Camden Yards

Baltimore, MD, USA

Building Trust in Real-World Evidence: The Role of Study Registration

Real-world evidence on treatment outcomes can be an important aspect of the evidence basis for decision making if it is seen as credible. For real-world studies that are meant to test hypotheses about comparative-effectiveness or safety, a key aspect of credibility is that they are conducted transparently with analyses that follow a prespecified analytic protocol. Preregistration of such study protocols on a public website would help build trust that their results can be used for decision-making purposes.

The 2019 Summit will be a forum for discussion of the work of the Real-World Transparency Partnership, led by ISPOR, International Society for Pharmacoepidemiology (ISPE), Duke-Margolis, and National Pharmaceutical Council (NPC), and involving a number of other organizations and stakeholders. It will focus on the key elements needed for the creation of a common registration site for these real-world studies that will be oriented for regular use by researchers and seen as a credible registry by decision-makers. The work already completed in this effort will be presented and the future steps envisioned will be discussed with Summit attendees. A white paper summarizing the initiative and recommendations will be publicly available for review and comment prior to the Summit.

Sessions:

Transparency in RWE — Time for a Unified Approach

This session will provide an overview of the history and goals of the RWE Transparency Initiative and why it is timely, as well as its work to date. This will include a summary of the white paper and its responses. It will cover fundamental aspects of this issue including credibility vs. transparency, characteristics of studies recommended for registration (ie, Hypothesis-Evaluating Treatment Effect [HETE] studies), the importance of reporting, and replicability and the totality of evidence.

Registration site(s) — Opportunities to Optimize

During this session, we will hear from representatives of three potential sites - clinicaltrials.gov, ENCePP, and Open Source Forum, regarding their current capabilities for registering retrospective observational studies and their plans in this area going forward. The potential to align on a common protocol template and what that might entail also will be discussed.

Nuts and Bolts of Fit-for-Purpose

This session will include discussion of a number of key characteristics of a registration site needed to achieve its desired purposes. These include: a "lockbox" capability, allowing time-stamped pre-registration without making details immediately available to the public, allowing for a period of confidentiality; protocol elements needed for pre-registration to sufficiently specify the hypothesis, its supporting rationale, and how it will be tested, in enough detail to allow transparency of intended vs. actual analysis performed; the level of detail of post-analysis reporting needed to enable replication of the analysis; and potentially other considerations.

Behavior Modification — Boosting and Nudging

In this session, aspects of registration related to the "behavioral" elements of pre-registration will be examined. What level of detail and attestation about "pre-looks" at the data are appropriate? What is the right balance between information required and overall feasibility — is some pilot testing called for? What external conditions on pre-registration would be the best incentives for encouraging its use?

Transparency in RWE — Moving Forward

This panel will reflect on the day's discussion and review the next steps needed to move towards making pre-registration common practice for RWD hypothesis-testing studies in light of both the opportunities and the challenges. There will be time for audience interaction.

Join us at this Summit to learn more about this initiative and help shape its work to come.

Register at www.ispor.org/Summit2019

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CONFERENCES & EDUCATION

Healthcare Digitalization Unpacked - Learn, Innovate, and Find Your "Hygge" at ISPOR Europe 2019


Gyrd-Hansen


Longson


Severens

Program Committee Co-Chairs:
Dorte Gyrd-Hansen, PhD, MSc, University of Southern Denmark, Odense, Denmark; **Carole Longson, PhD**, Association of the British Pharmaceutical Industry (ABPI), London, England, UK; **Hans Severens, PhD**, Erasmus University Rotterdam, Rotterdam, The Netherlands

Dear Colleagues and Friends,

We are very pleased to invite you to join us in Copenhagen for ISPOR Europe 2019, the leading European conference for health economics and outcomes research (HEOR). Given the acceleration of the digitalization of the healthcare landscape worldwide, this year's theme, *Digital Transformation of Healthcare: Changing Roles and Sharing Responsibilities*, is especially relevant. Rapid advances in information technology and data science—along with increasing emphasis on using real-world data and evidence to inform regulatory and healthcare coverage—raise questions regarding the ability of the healthcare ecosystem to adapt, critically assess, embrace, and even thrive given the opportunities that these advances hold. These issues and others will be addressed during the scientific program, which is highlighted by three plenary sessions.

The plenary sessions will focus attention on the incentives of the new players in the digital transformation and how roles are changing, the impact that the digital healthcare system can have on providers and patients, and emerging opportunities and challenges to creating real-time learning healthcare systems.

The first plenary, on Monday, 4 November, "Healthcare Digitalization: Instant, On Demand, and Always Connected," will address the rapid change affecting healthcare systems in real time, especially as to how care is organized and delivered. The panel will explore the objectives, incentives, and aspirations of the new players in digital transformation and how the roles of traditional stakeholders are changing.

The second plenary, on Tuesday, 5 November, "Shaping the Digital Healthcare System," will explore how the key "actors" in healthcare systems are adapting to the technological developments to deliver more productive, more effective, and more personal care for patients who are enabled by various digital technologies to actively influence their medical journey.

The third and final plenary session on Wednesday, 6 November, is titled, "Big Healthcare Data: Endless Opportunities for Research and Learning." Big data present a tremendous opportunity for the measurement and reporting of quality in healthcare and new methods are needed to harness the potential for these data to have real impact. Speakers will provide examples of using these tools not only for research, but also for driving learning at the healthcare-system level.

These plenaries are only one aspect of our scientific program. ISPOR Europe in Copenhagen offers opportunities for learning through a diverse short-course program on Saturday and Sunday, followed by innovative spotlight sessions, topical breakout sessions, and over 2500 research poster presentations. A new featured session, ISPOR Ideas Lab, will be launched in Copenhagen and is designed to fuel original views and fresh perspectives and to trigger and strengthen innovative thinking and the spirit of discovery in the HEOR community.

We are sure that both an outstanding scientific program and your curiosity to experience the authenticity of one of the most livable cities in the world will convince you to join ISPOR Europe this year. Copenhagen[1], labeled the "City for Life," will offer plenty of "hygge[2]" when you go for a walk or a bicycle ride after a day at the conference.

Copenhagen is large enough to offer a selection of 15 Michelin starred restaurants, but small enough to bicycle from one end to the other in 20 minutes. The city offers a vibrant urban pulse with plenty of Nordic cuisine and Nordic fashion amongst cobbled streets, castles, and bell towers. Take a stroll down one of Europe's longest pedestrian shopping streets (Strøget), and have beer and smorgasbord at the 17th-century waterfront, Nyhavn, or visit the hipster districts of Nørrebro and Vesterbro, where you will find interesting quirky shops and restaurants in streets such as Jægersborggade and Ravnsborggade, and plenty of nightlife in The Meatpacking District.

We look forward to joining you in Copenhagen as we gather to further ISPOR's mission of promoting HEOR excellence to improve decision making for health globally.

See you in the "City for Life!"
— Dorte, Carole, Hans

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2. https://www.visitdenmark.com/denmark/highlights/hygge/what-hygge

CONFERENCES & EDUCATION

ISPOR Europe 2019

Digital Transformation of Healthcare: Changing Roles and Sharing Responsibilities

2-6 November | Bella Center Copenhagen
Copenhagen, Denmark

Join more than 5000 global healthcare leaders at ISPOR Europe 2019 — an energizing meeting ground for sound science, robust methodology, relevant policy discussions, and multistakeholder perspectives.

ISPOR Europe 2019 in Copenhagen offers opportunities to debate value in healthcare beyond cost-containment and short-term interventions — strategic perspectives, scientific validity and diverse global experiences. During the five days of the conference you will:

- Learn about digitization, digitalization, and digital transformation in healthcare and explore their impact on HEOR.
- Present and debate your research results and ideas in an open and neutral environment.
- Advance your career while staying current on emerging trends and attending short courses.
- Engage with recognized global experts and network with colleagues, collaborators, and clients.

Conference Highlights Include:

37 pre-conference short courses

Offered in conjunction with ISPOR Europe 2019 these are a series of half- and full-day training courses, designed to enhance your knowledge and technique in seven key topic areas ("Tracks") related to health economics and outcomes research (HEOR).

9 NEW short course sessions include

ISPOR ESSENTIAL HEOR EDUCATION

- US Payers — Understanding the Healthcare SystemTM
- Fitting the Structure to the Task — Choosing the Right Dynamic Simulation Model to Inform Decisions about Healthcare Delivery
- Health State Utility (HSU) Recommendations for Identification and Use of HSU Data in Cost-Effectiveness Modeling
- Why All the Hype? Nordic Data Explained
- Digital Real-World Evidence Generation Approaches in Rare Diseases and Oncology
- Market Access & Value Assessment of Medical Devices
- Probabilistic Graphical Models with Openmarkov, an Open-Source Tool
- Creating Natural, Flexible Models with DICE Simulation
- Mapping to Estimate Utility Values from Non-Preference Based Outcome Measures — Part 2

CONFERENCES & EDUCATION

Plenary sessions

Healthcare Digitalization: Instant, On Demand, and Always Connected (Monday, 4 November)
An expert panel will explore the objectives, incentives and aspirations of new players in digital transformation of healthcare, how the roles of traditional stakeholders in healthcare are changing, and what needs to be done to strengthen the effectiveness of the change efforts in delivering desired results.

Shaping the Digital Healthcare System (Tuesday, 5 November)
In this session we will explore how the key "actors" in healthcare systems are adapting to the technological developments in healthcare (ie, genomics, artificial intelligence, digital and real-time medicine, robotics) to deliver more productive, more effective and more personal care for patients.

Big Healthcare Data: Endless Opportunities for Research and Learning (Wednesday, 6 November)
The final plenary will offer discussion of the need for innovative forms of information processing (ie, big data, social media, data analytics) to ensure enhanced insight and decision-making for the measurement and reporting of quality in healthcare.

Spotlight Sessions

Sessions will highlight timely topics in HEOR and promote areas of innovation of interest to the ISPOR community.

- Transparency in RWE — Time for a Unified Approach
- Genomics in the Future of Health — The Road to Better Outcomes?
- The Evolving Demands for Medical Device Evidence Development: What the Future Holds

ISPOR Ideas Lab

New Insights to Improve Decision-Making for Health Globally
The ISPOR Ideas Lab is designed to fuel original views and fresh perspectives. Topics include new thinking on "social determinants" and alternative perspective on the "O" and the "E" in HEOR, sustainability index to futureproof healthcare, and next generation HTA for complex and personalized combinations of health technologies. The session is designed to fuel original views and fresh perspectives and to trigger and strengthen innovative thinking and the spirit of discovery in the HEOR community.

- Ecosystems of Health Value: A Value Design Framework
- Futureproofing Healthcare: Improving the Sustainability of Healthcare Systems Through Data
- HTx — Next Generation Health Technology Assessment

Special Sessions

Two highlighted Issue Panels will bring together leaders in the field to discuss timely issues facing healthcare today.

- IP9: Transparency in RWE — Can We Navigate the Key Challenges?
- IP11: Cross-Border Collaboration on Availability of Pharmaceuticals in Europe — What, Why and What If?

2800+ Conference Presentations

Focusing on topics such as real-world evidence, digital health, health technology assessment, value assessment, medical devices, and patient preferences, featured in issue panels, workshops, forums, oral podium presentations and poster presentations and symposia.

Be an Exhibitor or Sponsor

Join the 100+ exhibitors and sponsors in the Poster and Exhibit Hall at Copenhagen. Your organization will get invaluable networking, business development, and brand recognition opportunities at ISPOR Europe 2019. Participate in the HEOR Theater and share your message with 30-minutes of valuable uninterrupted time. Benefits are provided at www.ispor.org/Europe2019sponsorship

Register at www.ispor.org/Europe2019Reg

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CONFERENCES & EDUCATION

Mark Your Calendars for 2020!

ISPOR 2020

May 16-20
Disney Coronado Springs Convention Center
Orlando, FL, USA

Join us for a 20-20 view of the state of HEOR today at ISPOR 2020.

We are planning a robust five-day program with two pre-conference days featuring the ISPOR Short Course program and 1800+ presentations in the forms of plenary sessions, advanced spotlight sessions, workshops, issue panels, forums, oral podium presentations, abstract poster presentations and symposia. You can continue your education by visiting the ISPOR Exhibit Hall meeting and speaking with industry experts and taking part in the Exhibitor HEOR Theater.

There will be plenty of networking opportunities with some of the leading names in HEOR today at the Women in HEOR events, Students and New Professionals events, welcome and networking receptions in the Poster and Exhibit Hall, the 2nd Annual Awards Banquet, and more.

Come early or stay late — bring your family and take advantage of the beautiful setting and surroundings of Disney's Coronado Springs Resort and all that Orlando has to offer.

Abstract Submission Opens: October 1, 2019
Abstract Submission Deadline: January 15, 2020
Registration opens October 2019

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CONFERENCES & EDUCATION

Partner. Participate. Progress.

Gain access to influential leaders and decision-makers in HEOR by sponsoring or exhibiting at ISPOR's conferences. ISPOR provides a platform for connecting with thousands of leaders and experts representing all facets of healthcare, including researchers and academicians, regulators and assessors, decision-makers, clinicians, industry, and patient representatives.

Exhibit Opportunities

The Society's conferences draw an audience of researchers and decision-makers from biopharmaceutical medical device, and diagnostics industries; payers, health ministries, government organizations, academia, and other healthcare organizations. Exhibit at a booth, table, and reserve your half-hour slot at our newest exhibitor offering, the HEOR Theater!

Sponsorship Opportunities

Increase your visibility and prominence in the field of HEOR by becoming a conference sponsor. Benefits can include conference and exhibit hall registrations and highlighted listings in the exhibitor directory. Sponsor a symposium, a charging lounge, internet or WiFi access, a coffee break, notebooks, lanyards and more!

Contact us for more information or to discuss specific conference sponsorship and exhibit opportunities at exhibit@ispor.org

Upcoming 2020 Events

ISPOR 2020

May 16-20
Orlando, FL

Abstract Submission Opens: October 1, 2019

Abstract Submission Deadline: January 15, 2020

ISPOR Asia Pacific 2020

12-15 September
Seoul, South Korea

Abstract Submission Opens: 2 December 2019

Abstract Submission Deadline: 11 March 2020

ISPOR Dubai 2020

29-30 September
Dubai, United Arab Emirates

ISPOR Europe 2020

14-18 November
Milan, Italy

Abstract Submission Opens: 2 March 2020

Abstract Submission Deadline: 10 June 2020

FROM THE JOURNALS

Section Editors: **Agnes Benedict** and **Soraya Azmi**

In our "From the Journals" section, we highlight an article from a recently published issue of either *Value in Health* or *Value in Health Regional Issues* that we hope you find informative as well as relevant.

Value in Health July 2019

CURATIVE THERAPIES

Uncertainty and Cures: Discontinuation, Irreversibility, and Outcomes-Based Payments: What Is Different About a One-Off Treatment?

Adrian Towse and Elisabeth Fenwick

The development of treatments potentially offering "cure" has raised several challenges for healthcare systems, especially for payers. These challenges include 1) affordability of "curative" treatments, 2) degree of uncertainty in health gains, 3) impact on market dynamics, and 4) risk-sharing payment mechanisms and pricing. In order to facilitate unbiased decision making, the advent of cures requires an in-depth assessment of existing methods of economic evaluations and the interpretation of their findings.

Treatments achieving a cure can be delivered as one-off or as repeated-dose (ie, requiring repeated administration). This article outlines the criteria for managing decision uncertainties around these 2 types of curative treatments. Firstly, uncertainty about health gains when considering new adverse evidence (such as where the cure only lasts for 3 years). One-off treatment cannot be discontinued as it is irreversible; whereas, repeated-dose administration can be discontinued. Secondly, the value of collecting information on long-term health gains is a provision in coverage with evidence development/adoption "only with research" (CED/OWR) schemes. One-off cures are irreversible; however, they can avoid widespread adoption. Lastly, payers and providers want to know about potential innovative payment models that can be used in risk-sharing.

The authors have presented a stylized example of managing decision uncertainty for curative treatments. An economic model was developed to assess the 2 deliveries of curative treatments compared to current standard of care (SoC). One-off and repeat-dose curative treatments are both assumed to be expensive and therapeutic, whereas the SoC is inexpensive but has no impact on mortality. The example is simplified by assuming that only the current prevalent population is treated; there is no incoming incident population. To alleviate the financial irreversibility of the one-off cost of curative therapy various payment mechanisms are proposed: an annual outcome-based "success" payment for each year for which the patient continues to benefit from treatment (ie, the patient is alive, and treatment continues to work), versus an annual annuity payment based on amortization, in which payment is made only for patients who are alive (ie, an payment scheme that is less sensitive to the treatment no longer working).

Cost-effectiveness and budget impact results are summarized, comparing uncertainties arising from one-off and repeat-dosage treatments and comparing the 2 payment mechanisms. The authors also present the cost-effectiveness acceptability curve (CEAC) and expected value of perfect information (EVPI) curve associated with one-off and repeat-dosage treatment. Generally, the degree of decision-making uncertainty (measured by EVPI) associated with one-off treatment is 4 times higher than that of repeat dosage ($160 million compared to $40 million, respectively) plus a probability of being cost-effective at a $50,000 threshold is 86% for one-off dosage, compared to 100% with repeat-dose treatment. The results show that the only difference between the 2 treatments is the discontinuation effect (ie, the irreversibility of payment should the one-off treatment stop working). The article concludes that prevalence and discrimination issues mean that the impact on the payer of an incorrect decision is greater with one-off treatment than a repeat therapy. With evidence collection, this risk diminishes over time (a form of CED or OWR). Financial arrangements or risk sharing can eliminate differences for the payer between one-off and repeat-dose therapy. Furthermore, market dynamics of the introduction of future competitive treatments can be used to pursue discounted prices that contribute to the affordability of treatments.

Even in the absence of a difference in uncertainty of outcomes, adverse payoffs differ. The greater financial risk associated with a cure is related to the issue of treatment discontinuation, driven by irreversibility. Pragmatic adjustments may need to be made to take account of cost-ineffective SoC comparators and of the potential impact of new entrants, which will change the price dynamics between the one-off and repeat forms of treatment.

In summary, this paper will be of interest to readers as it provides insight into how the results of economic evaluation one-off and repeat-dose potentially curative therapies will differ and what aspects warrant consideration in addition to traditional cost-effectiveness analyses. It outlines some criteria for managing decision uncertainty and provides a practical example to guide an unbiased economic evaluation for curative treatments. It also presents a new set of challenges related to irreversibility. The authors urge readers to look beyond the standard cost-effectiveness and budget impact results and delve deeper into the uncertainty around these treatments and potential ways to address them. Although both one-off and repeat-dose treatments could be cost-effective, the irreversibility of one-off treatments plays an important role in decision uncertainty. Collection of long-term data, introducing innovative payment models, and ensuring market dynamics can reduce the uncertainty and contribute to the affordability of these treatments.

AWARDS

ISPOR Scientific Achievement Awards – Call for Nominations

The ISPOR Awards Program is designed to foster and recognize excellence and outstanding technical achievement in pharmacoeconomics and outcomes research. These awards will be presented at ISPOR 2020, May 16-20, 2020, Orlando, FL, USA.

The ISPOR Avedis Donabedian Outcomes Research Lifetime Achievement Award

The ISPOR Avedis Donabedian Outcomes Research Lifetime Achievement Award is established in honor of the late Avedis Donabedian MD, MPH to acknowledge those individuals who have made a major contribution to the improvement of health outcomes. Nominations may be made by any ISPOR member. Members may nominate more than one person; however a completed letter of recommendation must accompany each nomination.
For complete details, see www.ispor.org/avedisaward.

ISPOR Marilyn Dix Smith Leadership Award

The ISPOR Marilyn Dix Smith Leadership Award is international in scope and stature. The Award recognizes one individual each year that has provided extraordinary leadership to the Society. It will be presented on a frequency determined by the ISPOR Marilyn Dix Smith Leadership Award Committee, but not more than one time per year. Nominations for the Marilyn Dix Smith Leadership Award require a letter of recommendation for the nominee, nominee's leadership contributions to the Society and nominee's CV.
For complete details, see www.ispor.org/mdsaward.

ISPOR Bernie O'Brien New Investigator Award

The ISPOR Bernie O'Brien New Investigator Award was established in 2004 to honor the long-standing commitment of Bernie J. O'Brien, PhD to training and mentoring new scientists in the fields of outcomes research and pharmacoeconomics. All nominations must include a letter of support for the nominee and a current edition of the nominee's CV essay indicating the reason for your nomination.
For complete details, see www.ispor.org/obrienaward.

ISPOR Health Economics and Outcomes Research Excellence Award-Methodology
ISPOR Health Economics and Outcomes Research Excellence Award-Application

The ISPOR Award for Excellence in Methodology and Application were established in 1997 to recognize outstanding research in the field of health economics and outcomes research methodology and outstanding practical application of health economics and outcomes research in health care decision making. Members may submit nominations (either their own publications or others). All nominations must include a brief cover letter indicating the reason for the nomination. Supporting documentation MUST include a PDF of the nominated paper.
For complete details, go to www.ispor.org/awards.

ALL NOMINATIONS DUE BY FEBRUARY 7, 2020

Nominations can be submitted at www.ispor.org/awards

For more information, contact Stephen Priori: spriori@ispor.org

AWARDS

A Futurist for HEOR, Data Management, and Healthcare

Marc L. Berger, MD, the winner of ISPOR's Avedis Donabedian Outcomes Research Lifetime Achievement Award for 2019, is semiretired, with emphasis on the "semi" part. After a long career spent with Merck & Co., Eli Lilly and Co., OptumHealth, and Pfizer Inc., he has more time to spend with family and to travel. But as a consultant and a volunteer with ISPOR's task forces, and the author of more than 130 journal articles, book chapters, and other publications (including in *Value in Health* and the *New England Journal of Medicine*), Dr. Berger continues to look to the future.

Although he has made many contributions to the health economics and outcomes research (HEOR) fields, being given the Donabedian Award came rather as a surprise. "I was surprised that I got it; there are many wonderful candidates out there," Dr. Berger says. "And any time you get an award, there's a combination of pride and embarrassment mixed up with it."

"I think this award is a statement that I have been a useful contributor to the ongoing conversation around health economics, outcomes research, health policy, and related fields."

Although most of his career was spent at Fortune 100 companies, Dr. Berger always considered ISPOR his second home.

"ISPOR has been a place where I have been able to do some of the most satisfying things in my career—working on various task forces and being part of conversations that have helped move the field forward," he says. "And ISPOR has been involved in and is at the forefront of thinking [about] what is the intersection between good health economics, outcomes research and health policy."

A CAREER SPENT IN INNOVATION

Dr. Berger didn't intend to do health economics or outcomes research. He wanted to become a physician and a basic scientist, starting off by doing academic work on the mechanisms of liver cell injury and repair. But he decided to make a career switch after his employer at the time, the University of Cincinnati, had him doing less research and more clinical and teaching work. And with a family, he needed to make the leap into corporate life.

Merck was his first stop, where he initially got involved in phase II and phase III clinical research. Some of the projects he worked on included bringing another formulation of the proton-pump inhibitor omeprazole to market as PRILOSEC and bringing the antacid famotidine (Pepcid) over the counter. About this time, during the Clinton administration, "Bill and Hillary's healthcare reform 1.0" was introduced, with the consequential rise of managed care, Dr. Berger says. "Everybody was talking about what are we getting from the healthcare system, what we're investing all this money in."

After switching from clinical research, he helped create the new outcomes research management group at Merck. The group was led originally by Rob Epstein, who was recruited by Dr. Berger. But Epstein, an early president of ISPOR, left a year after the group was formed to become chief medical officer at Medco.

"I was left with a very small group, none of whom were trained in the area, and I rapidly recruited a stellar group of people that was just fantastic to work with," Berger says. Among his recruits were Leona Markson, a health services researcher; Tom Abbott, a health economist; Jim Murray, an industrial engineer (who Dr. Berger later recruited to Lilly); and X. Henry Hu, an epidemiologist.

"With this group of people, we just started doing lots and lots of really good research," Dr. Berger says. "At that time, we arguably built probably the largest and best outcomes research group in the industry. We did research in everything that was overlapping the interests of Merck as a company, but also was just really interesting and good things to be working on and exploring a lot of different areas."

Among the group's research was work on the use of bone density testing for the diagnosis and follow-up for osteoporosis and what Dr. Berger called "groundbreaking" work in how to build disease-management programs. "We did some important work that contributed to the discussion about how cost-effectiveness research should be utilized in health policy decision making. We did some work on the impact of chronic health conditions on productivity in the workplace and published some seminal articles in that area. It was a wonderful and heady time."

But then Dr. Berger decided to move on, heading to Lilly, where he faced a different challenge. There, he had to learn how to bring all the different groups across the company together into a coherent collaboration that would help focus Lilly on having a clear value story for the products it was bringing to market.

"That was an organizational challenge as much as anything else, as well as changing a bit of the culture within Lilly to embrace the fact that every product needed to have a clear value story and we would have to know what it was in advance as you developed the product, and not wait until we got to market in order to provide evidence for the story," Dr. Berger says.

After Lilly, Dr. Berger got a glimpse on the payer side when he went to work

as a senior scientist for a brief time at OptumHealth, where he was able to understand in greater detail how a payer thought about its mission: to provide healthcare for a covered population and maximize the impact of the dollars invested.

"That was a very useful perspective, and sometimes I found out the answer was quite straightforward," he says. "Like, 'Sure, we'd love for our patients to be directed to physicians, or providers, or hospitals where they get the best outcomes for the least amount of cost, and if we can direct patients to those centers, that's win-win, that's a no-brainer.' But it's not always possible to do that, and the idea of how you inspire all of the providers in your network to provide better-quality healthcare and use resources most efficiently, is a heavy lift."

Leaving Optum Health and going to Pfizer, Dr. Berger found an even more-interesting challenge.

'I had done a lot of research using existing healthcare databases and I understand a lot about the nuts and bolts of good methodology for outcomes research, and in fact had been on several task forces for ISPOR to extol best practices for how to do those methodologies," he says. "But I hadn't really spent a lot of time looking under the hood of how do you actually get this data, manage it, and make it accessible for analysts."

At Pfizer, Dr. Berger created a new group, Real World Data and Analytics, where he had to tackle the problems with building a central data mart that would make the data more easily accessible and better able to be interrogated.

"That's when I got deeply involved in understanding what information technology groups do, and different architectures for housing the data and how one may begin to interrogate that data but in a different way," he says. The solution was to merge existing data analytics products into a "best of breed" solution in which data could be interpreted via drag-and-drop, object-oriented programming.

Dr. Berger says Pfizer's centralized data mart and ways of analyzing data have been emulated by many other countries across the industry. Ultimately, "All of that work depends on having better strategies to house, combine, and interrogate these real-world data sets," he says. "And so, to me, relatively late in my career, I was an old dog that had to learn some new tricks. We helped usher in what is supposed to be a new golden era of analytics on real world data."

LIFE AFTER RETIREMENT: THE FUTURE OF HEOR

Since retiring from Pfizer, Dr. Berger says he has spent a lot of time with family, including his 4 grandchildren. In addition, he has traveled. "I've taken 2 big trips, I've been to Antarctica, I've been to Southeast Asia. I've got more goals, there are many more things I'm going to do," Dr. Berger says. "But I'm also trying to be a little bit of a provocateur about what is the future going to look like. I am being a little bit of a futurist."

As a consultant, he has preferred being an advisor to several health IT companies such as SHYFT Analytics "because they're the ones that are building the future." He also continues working with ISPOR's task forces on real-world evidence and writing articles.

One of his recent papers, written with Don Husereau for the anniversary issue of *Value in Health*—"Looking Backward: 2143 to 1943, The Rise and Fall of the RCT"—theorizes how the fields of information technology, basic science, and clinical research will change healthcare over the next 130 years.

"We expect that there will be ubiquity of data, and of all kinds of data, including data from implantable or wearable sensors, and that there are going to be breakthroughs on our understanding of the science of the mechanisms behind disease," Dr. Berger says. "And we assume that there's going to be breakthroughs in artificial intelligence way beyond what we've seen today. And a mixture of those 3 is going to enable us to have a much more efficient and effective healthcare system that will truly be what people envision when they talk about a learning healthcare system."

In such a system, doctors will do things that only doctors can do and things that they don't have to do will be taken over by either artificial intelligence or other healthcare providers. And the authors speculate that by the end of the century, standalone controlled trials will no longer be needed as they will be effectively embedded into the order of care with consent becoming automated.

According to Dr. Berger, the field of outcomes research has a clear path forward.

"Outcomes research is not going to be just people who are trained in health services research, outcomes research, and epidemiology," he says. "It will be increasingly done by data analysts. And so, outcomes researchers need to become much more familiar with these newer, advanced analytic techniques because it's going to change how we explore important questions."

For example, he believes that the future is going to go beyond the regression model. "It's going to be some form of machine learning or something that develops out of machine learning. They need to become much more nimble in terms of how they're thinking about analytics, and not remain wedded to what has worked for the last 50 years."

Above all, a disruptive change is coming to all of healthcare, not only to the value frameworks, but the pharmaceutical industry, the payer/insurance industry, and all the way cross the board.

"Ultimately the motivating force is going to come from citizens and patients who are going to recognize that the system needs to change dramatically if it's going to meet their expectations," Dr. Berger says. "This is going to be a political conversation as much as it's going to be a scientific conversation."

Anticipating the Impact of an Aging World

This past July 11, 2019, marked World Population Day, an event established by the United Nations Development Program to call attention to the impact of population changes.[1] This year's World Population Day highlighted a major demographic shift. For the first time in human history, the global population now skews old with more people over age 65 than under 5. And this trend is expected to continue—by 2050, the number of persons over 65 will be double the size of this youngest cohort. An aging population will mean huge increases in demand for health services and increasing pressure on already limited resources.

By Michele Cleary

As longevity far exceeds the typical work lifespan and as birth trends reduce the number of taxpayers needed to sustain government budgets, stakeholders must rapidly consider new approaches to improving health status and/or reducing health resource utilization if healthcare financing systems are to sustain this ballooning elderly population.

This article presents some of the demographic trends that are impacting the health systems around the world before proposing some possible solutions to extend healthy living and minimize economic demands.

THE SIZE OF THE GRAY TSUNAMI

Despite an estimated 83 million people added to humanity each year, our global population is rapidly becoming increasingly old—very old. Today, 8.5 percent of people worldwide are at least 65 years old. This segment is expected to balloon to nearly 17 percent by 2050—1.6 billion people over 65 by 2050. Even more astonishing is the expected growth of the "oldest old"—people aged 80 and older—whose numbers are expected to more than triple by 2050, growing from 126.5 million to 446.6 million.

While this "graying" of society has long been a concern in many developed countries, aging is a global trend. The developing world is also growing older. China's population of persons over 65 will swell from 110 million today to over 330 million by 2050. However, this demographic shift is still years away in the developing world. For instance, while Japan's oldest population surpassed its youngest in 1978, the Sub-Saharan region of Africa will not do the same until 2079.

THE IMPACT OF FERTILITY CHANGES, GROWING LONGEVITY

This demographic shift has been driven by changing fertility rates—both booms and busts—and remarkable increases in life expectancy.

Fertility: Much of the developed world experienced a spike in fertility rates during the mid-20th century, creating an enormous population cohort that is just now reaching old age.[2] The Baby Boom dramatically increased the birth rates across the United States, Canada, New Zealand, Australia, United Kingdom, France, Austria, Scandinavia, Czech Republic, and Latin America, while smaller "boom-lets" echoed across Germany, Switzerland, Belgium, and the Netherlands. It's notable that this trend was largely absent from Italy, Greece, Portugal, Spain, Poland, Bulgaria, Russia, Estonia, and Lithuania. Since then, global fertility rates have dropped to near or below replacement levels in all regions except Africa.

Longevity: The other population driver has been increased longevity. Since the Age of Enlightenment, the average global life expectancy has steadily climbed. In the pre-modern world, life expectancy hovered around age 30. By 1900, few babies lived past 50 years. Today, average global life expectancy exceeds 72 years and is projected to climb above 76 years by 2050.[3]

Nowhere have these gains been greater than in Africa, where life expectancy has gained nearly 7 years since 2000 (it rose only 2 years throughout the 1990s). Dramatic increases have also been shown in India and South Korea where a century ago life expectancy hovered near 23 years for both countries, but has since nearly tripled in India and almost quadrupled in South Korea.

Gaps in longevity persist between the developed and the developing world. However, these gaps are closing, and they are projected to diminish significantly by 2050 thanks to aggressive measures to combat childhood mortality and broad initiatives to fight human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) and other infectious and noncommunicable diseases. While many of these measures have significantly reduced disease burden, especially in young children, rates of disease burden (as measured by daily adjusted life-year [DALY] loss rates) remain highest in the youngest and oldest population groups with DALY loss rate remaining highest among the oldest old.[3]

SHIFT FROM COMMUNICABLE TO CHRONIC, NONCOMMUNICABLE CONDITIONS

During the 20th century, the leading causes of disease and death changed dramatically, shifting from infectious and parasitic diseases to noncommunicable diseases and chronic conditions. The multi-country Global Burden of Disease Project revealed that health problems typically associated with wealthy and aged populations now impact a widening segment of the global population as health behaviors commonly associated with the developed world (eg, tobacco and alcohol use, insufficient consumption of vegetables and fruit, low levels of physical activity) take root in the developing world. Over the next 20 years, global rates of noncommunicable diseases, such as heart disease, cancer, chronic obstructive pulmonary disease (COPD), osteoarthritis, and diabetes are projected to increase dramatically.[4] And as developing countries adopt more Western diets and lifestyles, the incidence of cancer is expected to accelerate; the number of new cancer cases is projected to rise to 17 million each year by 2020 and to 27 million by 2030.

And yet despite the tremendous impact of these noncommunicable conditions, communicable diseases, such as influenza, will continue to pose a significant health threat to older individuals. The World Health Organization has highlighted the continued threat of communicable diseases, especially in crowded environments. Future older cohorts will be highly susceptible to infectious diseases due to their immunosenescence—the progressive deterioration of immune function with age—and frailty.

GROWING IMPACT OF DEMENTIA

Dementia will also present a tremendous challenge to these aging populations. The Organization for Economic Cooperation ›

and Development summarized how the risk of dementia increases sharply with age. The prevalence of dementia increases from 3 percent among persons aged 65 to 69 to almost 30 percent among persons aged 85 to 89 years. Roughly 81percent of people with dementia are over age 75.

Alzheimer's Disease International projects that 115 million people worldwide will be living with Alzheimer's disease or dementia in 2050.[5] This growth will be most dramatic in low- and middle-income countries, increasing from 20 million today to nearly 80 million people with dementia by 2050. For these countries, healthcare labor demands associated with dementia and other memory loss conditions will put further tremendous strain on their future financing systems.

TOO FEW PROVIDERS, TOO FEW CAREGIVERS

One significant challenge will be finding enough providers and caregivers—paid or unpaid—to care for this aging population. Many are predicting staggering healthcare labor shortages. The American Association of Medical Colleges predicted that the United States will face a shortage of between 40,800 and 104,900 physicians by 2030.

Families are unlikely to fill this labor gap. Historically, the elderly may have had family support to monitor nutrition, health events (stroke, falls, accidents, heart attacks), and medication adherence to ensure health and quality of life. But today, fewer older people have families to care for them due to a range of issues: decreased family size, female labor force participation, high divorce rates.

This shift in demographics and disease means that there will be a huge increase in patients who require longitudinal management of their progressive diseases rather than incident care for intermittent sickness and injury.

Already many elderly live alone, especially in developed countries. Nordic countries have the highest levels of elderly women and men living alone, between 45 percent and 50 percent for women and close to 25 percent for men. With declining support from families, society will need better information and tools to ensure the well-being of the world's growing number of older citizens to help expand independent living.

HITTING THE BUDGET CEILING

Globally, health systems will strain to meet the needs of aging societies. During ISPOR's 2018 Asia Pacific conference, Toshihiko Takeda, former Directory-General at the Health Policy Bureau at Japan's Ministry of Health, Labor and Welfare, summarized how Japan is contending with an aging population—a preview for the rest of the world.[6] He noted that the portion of Japan's population over age 65 has grown from 5 percent in 1950 to nearly 27 percent. This aged sector is predicted to grow before peaking at 38 percent in 2065. Among developed countries, South Korea is expected to reach a similar peak in 2065 following an even more rapid demographic shift (from 10 percent in 1980 to 37.7 percent in 2065). He compared this growth trend with those predicted for the United States, United Kingdom, France, and Sweden, noting that for each of these countries, the percentage of elderly should peak at roughly 25 percent by the mid-2030s.

He continued, outlining the significant budgetary deficits Japan now faces due to the booming social security expenditures (pensions, medical costs, welfare) and the falling tax revenues stemming from a shrinking working population relative to the number of retirees. He noted that this is further challenged by the adoption of advanced medical technology coupled with labor shortages.

While Dr. Takeda's presentation may provide a preview for the rest of the world, many countries already lack the tax base, pension systems, or insurance payment systems to pay for increasing health services demanded by an aging population. In the United States, 10,000 individual Baby Boomers retire each day, removing more taxpayers to pay for the care of the elderly. The global financial crisis of 2008 has limited the ability for many European countries to respond to these growing needs. This crisis forced Greece, Spain, Italy, and Portugal to reform pension systems, increasing the retirement age, limiting the number of benefits, and reducing resources allocated for healthcare and social care. Working lifetimes may need to be extended elsewhere around the world to parallel increasing longevity.

These financial demands will hit developing countries especially hard as their populations become old before their societies become wealthy. France had almost 150 years to adapt to a doubling of their over-60 population from 10 percent to 20 percent. Places such as Brazil, China, and India will have slightly more than 20 years to make the same adaptation.

FINDING SOLUTIONS

This shift in demographics and disease means that there will be a huge increase in patients who require longitudinal management of their progressive diseases rather than incident care for intermittent sickness and injury. Debate continues over whether societies can achieve a "compression of morbidity" and hold down health and societal costs through better public health initiatives, vigilant screening programs, and efficient treatment of chronic conditions.

Healthcare budgets will have limited capacity to accommodate these growing needs of a rapidly aging population. New solutions are needed. Some countries are focusing on disease prevention measures to expand healthy years of life, such as Croatia's Guide for Healthy Aging. Others are exploring new elder-friendly environments to meet the needs of their growing population of elders, such as age-friendly cities and adapting traditional services and products to meet new consumer needs. And many are exploring mHealth (including telemedicine) solutions that encourage a more active role for patients in their conditions, prompting medication and therapy adherence,

and providing fall detection as well as more efficient delivery of services, especially to home-bound seniors.

Innovative solutions, such as mHealth (telemedicine) and digital health (apps/wearables/monitors), can help treat people in place at home or in a nursing facility.[7] These solutions could help prolong independent years by encouraging healthy behaviors (eg, smoking cessation, dietary changes, weight management). They can help patients adhere to treatment protocols with clinical appointment reminders and daily medication management. Providers could obtain real-time patient information, remotely monitor vitals, alerting providers of possibly serious health events. And they can summon help in the event of a fall.

These solutions will need to meet seniors where they are by working within their physical and cognitive limits, especially if seniors are living independently.

In the previously mentioned talk, Dr. Takeda was optimistic that artificial intelligence (AI) and other new technologies could also improve productivity as Japan contends with their growing healthcare financing challenges stemming from an aging population.

SOLUTIONS MUST CONSIDER HEALTH LITERACY AND COGNITIVE LIMITS

These solutions will need to meet seniors where they are by working within their physical and cognitive limits, especially if seniors are living independently. Cognitive and mental impairments are common among the elderly, particularly among the oldest old, which can lead to a lack of social support, failure to follow medical treatment plans, inability to perform self-care, and increased need for structured supervision and institutionalization. Physical impairments, such as hearing and vision loss, may also compromise the impact of these solutions. Solutions must address these inherent limitations.

Many older individuals will struggle with diminished health literacy—a factor found to be associated with risk of all-cause mortality among older adults. Patients with low health literacy use emergency services more frequently, have higher healthcare costs, and utilize preventive services less frequently.[8] But the 2003 National Assessment of Adult Literacy estimated only 3 percent of older adults aged 65 and older were proficient with health literacy skills.[9]

WHERE ISPOR STANDS

For 2 years in a row, ISPOR members have voted "aging" to be one of the Top 10 HEOR Trends. ISPOR special interest groups in medical technology/medical device, medication adherence, clinical outcomes assessment/patient preferences, and nutrition can provide added research focused on aging trends and their impact on health and health services utilization patterns. Knowledge of the social environment is critical for the large number of elders who have limitations in mobility or self-care; it is also essential for ensuring that prescribed medical regimens are delivered correctly in both home and community settings. Data on the physical environment are important as well for minimizing falls, injuries, and the progression of disability and, in some cases, for preventing deaths from climate-related causes. Finally, innovative sources of real-world evidence may be needed to identify areas for improvements to improve diagnostics and treatment adherence.

CONCLUDING THOUGHTS

Healthcare systems and policymakers need to start planning now to cover costs and delivery issues before the system reaches the breaking point. How will aging affect healthcare and social costs? How will population aging play out differently for low-income countries that will age faster than their counterparts have, but before they become industrialized and wealthy?

Health economics and outcomes research will be critical to decision-support structures that determine how limited resources will be distributed. By focusing more attention on these issues today, stakeholders may be able to develop high-impact solutions that can both improve and preserve health for all demographic groups.

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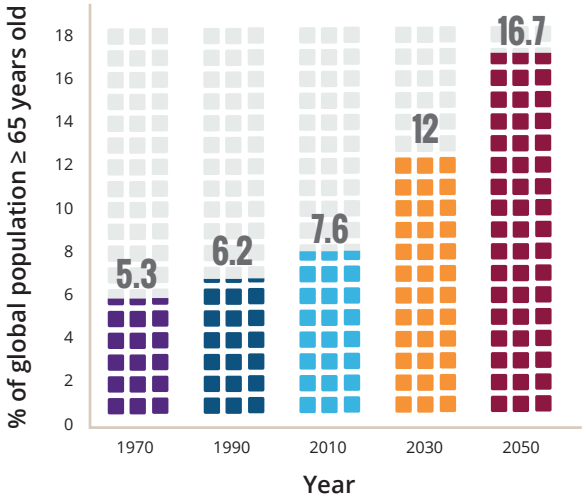
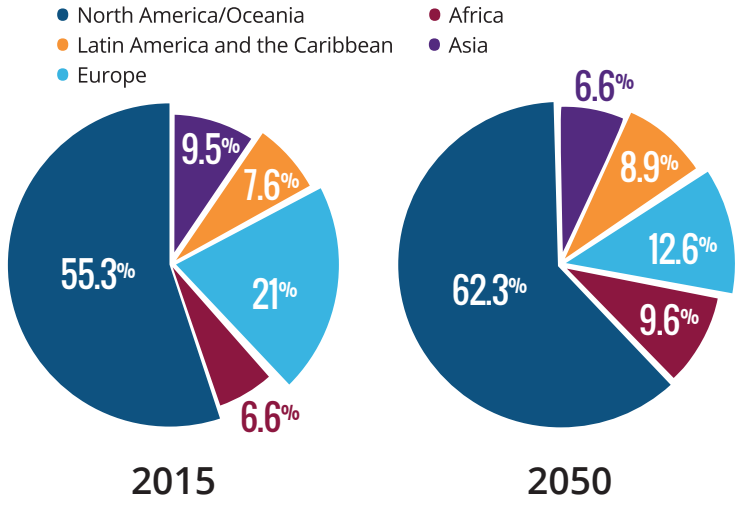
By the Numbers: Aging of the Global Population

Section Editor: The ISPOR Student Network

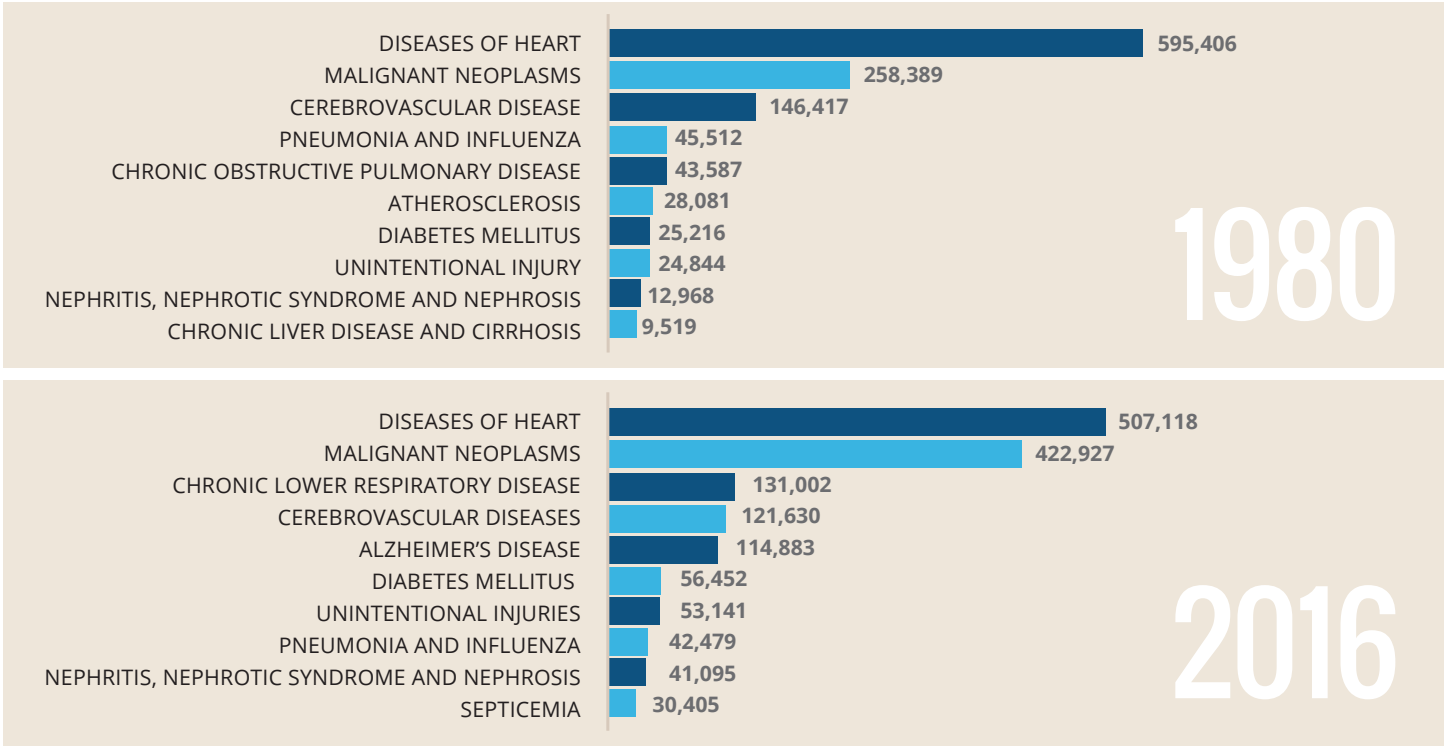
Global Population Aging Projections (≥ 65 Years Old)[1,2]



Percentage Distribution of the Global Population ≥ 65 Years Old by Region[3]



Top Ten Causes of Death Among Individuals 65 Years or Older in the United States (1980 vs 2016)[4]



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Aging of the Global Population: Implications on Healthcare and Provisions of Cost-Effectiveness

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At the forefront of population aging, Japan has faced a significant challenge ahead for the healthcare and economic system as a whole, as shifting attitudes and approaches toward health promotion and caring for the elderly population in Japan are offering new ways forward in managing the overall effectiveness and efficiency of the health system.

Population aging, as characterized by low fertility and mortality and longer life expectancy, is a significant achievement of public health and social development. Recently, with the profound demographic and epidemiological transition, unprecedented population aging has transcended regional boundaries and greatly influenced healthcare and public financing. It inherently and inevitably entails increasing disease burden and expanding demands of healthcare and social welfare services due to declines of intrinsic capacity, triggering a pessimistic anticipation of its detrimental effects on labor productivity and economic growth in a traditional sense.

At the forefront of population aging and with over a quarter of the entire population aged 65 years and above, Japan has been striving to address sustainability of its healthcare and social security system while harnessing the full potential of the citizens, including the seniors. Relevant experiences suggest that productivity and well-being of seniors could be improved by effective interventions promoting the positive and dismantling the negative determinants in health behaviors and social environment throughout the life course in a robust health system.[1] The concept of healthy, active aging has gradually shifted the stereotype of the elderly as frail and dependent; now it is no longer a rare phenomenon to see seniors enjoy substantial physical, cognitive, and functional well-being at their eighth, ninth, or even centenarian celebration. The super-aging society has brought tremendous changes on social value and policy portfolio.

Cost-effectiveness evaluation is a powerful tool to inform investment in health. This past April, after a trial run that started in 2016, Japan has formally launched a cost-effectiveness evaluation of the health insurance scheme. Underlying such movement toward promoted value-based healthcare are soaring health expenditures as the result of population aging together with technical advancement, in which exorbitant costs of advanced medical products and related treatment—eg, immunotherapy—are of major concern. The new approach is expected to leverage sustainability of universal healthcare and medical technology innovation. Although the current cost-effectiveness evaluation in principle targets pricing of medicines and medical devices, it has been argued that health technology assessment (HTA), comprehensively capturing outputs while weighing inputs of healthcare based on the value of patients and citizens, should be widely applied to pricing of clinical practices in the national medical fee scheme, community health planning, and reform of healthcare facilities.[2] Regarding this board sense of HTA, which subjects encompass a variety of medicines, medical devices, clinical practices, public health interventions and systems aiming health goals in the population, it is crucial to generate up-to-date methodologies and evidence assessing multifaceted outcomes/impacts with consideration for social and policy contexts in Japan.

Cost-effectiveness evaluation needs to present the changing value of healthcare in a more-broadened horizon. Today, the principle function of healthcare is no longer limited to facility-based clinical treatment, but rather an integration of both facility- and non-facility–based cares covering health promotion, prevention, treatment, rehabilitation and palliative care, and distinctions between healthcare and social welfare services have become more and more blurred. For example, the utilization of home-based care has dramatically increased during the past decade, for which most cases are aged above 75 years, and now more than half of the seniors prefer their home to facilities as the place for their final days. Responding to the increasing demands, the government has committed to strengthen an integrated support and care system at the community level by 2025, which constellates all relevant functional sectors of living, healthcare, nursing care, health promotion/prevention and daily life supports.

> **"Cost-effectiveness evaluation, potentially with the expanded horizon and the updated methodological strengths, is now expected to play an even more crucial role to guide and shape policies for constructive responses to healthy and active aging than ever before."**

Meanwhile, solutions for better health conditions in older age are not at the contemporary phase, but at an early stage of life; the physical and social environments that people live in and health behaviors throughout life such as a balanced diet and physical activities profoundly influence development of diseases and geriatric syndromes, and consequently, productivity and well-being in later life, as indicated by previous empirical evidence. Regarding the life course strategy for healthy and active aging, at macro level, as health intertwines with other social sectors and the economy, the benefits that the improved productivity of the elderly and the expectant nursing caregivers bring to growth and distribution are anticipated, especially in

the current policy context of a comprehensive public investment strategy to boost economic growth called, "Japan's plan for dynamic engagement of all citizens." These benefits include both health and nonhealth aspects, both senior people and their nursing caregivers, both the current and the next generations, as well as both the short-term and the long-term. Especially, the long-term impact of a life course strategy on population health, productivity, and well-being at both micro and macro levels is substantial in health economic outcome measurement.

On the other hand, several limitations have been raised from the current methodological framework. One of the most argued is that quality-adjusted life years (QALYs), a widely accepted generic measurement of health outcomes incorporating both length and quality of life, has limited power to capture various aspects of the health benefits and fails to reflect equity and distributional issues in social preference.[3] In the era of an aging society with pluralistic values of healthcare and social preferences as mentioned above, future research will be necessary to develop multi-criteria measurements integrating multidisciplinary knowledge and representing relevant stakeholders and aspiration levels both in Japan and also at the global level.

To this end, it is worthy to note the importance of boosting collaborations across disciplines, professionals, and regions, developing human resources and fostering a culture of value-based decision making in social and policy contexts.[4] Cost-effectiveness evaluation, potentially with the expanded horizon and the updated methodological strengths, is now expected to play an even more crucial role to guide and shape policies for constructive responses to healthy and active aging than ever before.

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The opinions presented in this article are based on the individual's view and do not reflect the view of the National Institute of Population and Social Security Research, Japan.

Population Aging: Conquest or Problem?

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The generation of a health care structure that meets the needs of increasing old age involves the capacity to respond to new forms of remuneration of the service. Changing demographics will require companies to rethink their workforces and understand that providing longevity to our population also requires creativity.

One of the greatest achievements of mankind was the extension of life expectancy, which was accompanied by a substantial improvement in the health parameters of the populations, although these achievements are far from evenly distributed in different countries and socioeconomic contexts. Reaching old age was once the privilege of the few, but today it has become more common even in the poorest countries. This major achievement of the 20th century has, however, become the great challenge for the present century.

Currently, Brazil has a total population of 208 million people; by 2060, the percentage of people over 65 years will increase from 9.2% to 25.5%. So, 1 out of 4 Brazilians will be elderly, according to the Brazilian Institute of Geography and Statistics (IBGE) data released in 2018.[1]

According to the survey, the percentage of people over 65 will reach 15% of the population in 2034, surpassing the 20% barrier in 2046. In 2010, it was at 7.3%. Among the consequences of an aging population, in addition to the inevitable increases in healthcare and pensions spending, IBGE highlights the highest percentage of people out of working age and therefore, dependents. Projections for Brazil estimate that the number of people being cared for by nonfamily members (formal caregivers) will double by 2020 and will be 5 times higher by 2040 compared to 2010.

The first step concerns the creation of a healthcare structure that meets the needs of a fragile age group in terms of health. This requires a broad range of services, from primary care (monitoring of blood pressure, diabetes, rheumatologic diseases, and cancer early detection), physical activities, and education to increase resilience, through the organization at secondary level with several specialists and gerontology professionals

in the areas of health. Finally, the tertiary care also needs attention, since they will have more diseases and complications, hospitalizations, and intensive care procedures.[2]

Whenever healthcare is an issue, alternative care models and new forms of service remuneration have long been imperatives in the central discussions of the health sector. The desired increase in system resolution and the effectiveness of health actions, both in the public and private systems, are clearly dependent on the changing logic of payment for services and the rationality that guides care models. The healthcare models adopted in the country have deep roots in the biomedical, vertical, and hierarchical models, with levels of increasing complexity of the services and inducing the overvaluation of services of greater technological density, inherited from Social Security Medicine and in the model of collective healthcare, originating from the sanitary and epidemiological surveillance of the beginning of the century.[3]

The fertility rate should also continue to fall in Brazil. Currently, it is 1.77 children for each woman. In 2010, it was at 1.75 and reached 1.8 in 2015. According to the projection, it should fall to 1.66 in 2060. The average age at which women have children is currently 27.2 years and, according to IBGE, will reach 28.8 years in 2060. The projection for Brazilian life expectancy at birth—currently 72.74 years for men and 79.8 years for women—is to reach 77.9 years for men and 84.23 years for women in 2060.

In the long run, population reduction also impacts the number of people of reproductive age. This is already the case in European countries, where fertility rates are very low and, consequently, there is a small number of people of working age. Therefore, it is necessary that these individuals receive incentive to have children to ensure that the population will sustain the elderly because the number of older people will continue to increase. Public policies cannot focus only on the elderly, as it would be impossible to maintain a good quality of life for them without major investments in children, young people, and adults of working age. Investment in health, education, and "full employment and decent work" is essential to ensure intergenerational solidarity.

In order for the elderly of today and tomorrow to have better quality of life, rights must be guaranteed in matters of not only health, but also work, social assistance, education, culture, sports, housing, and transportation. In Brazil, these rights are regulated by the National Policy of the Elderly, as well as the Statute of the Elderly, sanctioned in 1994 and 2003, respectively.[4] Both documents should serve as a beacon for public policies and initiatives that promote a true better age.

Thus, the organization of the health system is not able to fit the different indicators. The magnitude of the increase in health expenditures with old age depends, above all, on those who are healthier or free from illness and dependence. The prevention, independence, autonomy, and delay of diseases and frailties earlier in life are more relevant to the health of the aging population.[5]

On the one hand, the elderly present a greater burden of diseases and disabilities and use health services through existing models that present inefficiencies and high costs in times of new and innovative technologies. On the other hand, the process of reducing profits and losses to social security and growth and the opportunities that this demography presents are endless for the goals of an economically active older population. Older workers have skills, technical skills, and tacit knowledge—accumulated over the time of service—and can help younger people find ways to work safely and financially sound through guidance and information sharing. Today's older adults seek meaning and purpose, disrupting retirement norms and expressing increasing interest in lifelong work and volunteering.

In order for the elderly of today and tomorrow to have better quality of life, rights must be guaranteed in matters of not only health, but also work, social assistance, education, culture, sports, housing and transportation.

Changing demographics will require companies to rethink their workforces but will also create opportunities for nimble firms. For example, these changes will create opportunities in the food industry (an aging population will want to stay healthy and also may need more services such as home catering) and financial services (to plan for increasing longevity).

The longevity dividend, like most economic benefits, is possible, but it needs to be worked out. Using the skills of older workers, employing these workers more, and fostering intergenerational solidarity will mean that increased life expectancy can be very positive, both socially and economically.

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Aging Populations in Latin America, Healthcare and Pension Systems Challenges: Opportunities for Health Economics and Outcomes Research (HEOR)

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The Latin American elderly population might experience the largest increase compared with any other region worldwide before 2100, challenging not only the fiscal sustainability of public pensions but also healthcare systems in the region.

The Latin American population is aging fast, following the worldwide demographic transformation driven by life expectancy rise and fertility decrease, 2 processes of enormous economic and social impact.[1] Population aging is challenging not only for the fiscal sustainability of public pension but also for healthcare systems in the region.[2]

UNDERESTIMATION OF OUR STATISTICAL SYSTEMS

One of the main challenges for Latin America is to have accurate statistical systems to allocate resources properly and adjust policies to the needs of this growing age group. According to a study conducted in Colombia, in 2014, the Individual Registries of Health Services Provision (RIPS in Spanish) reported a greater population of people aged 80 years old or more than the projections made by the National Administrative Department of Statistics (DANE in Spanish) for that same age group.3 One possibility is that DANE projections underestimated the growth of this population group.[3] Therefore, more acute statistical systems are needed not only in Colombia but also in the entire region.

CHALLENGES FOR PENSION SYSTEMS

Latin American spending on pensions remains relatively low: less than 4% of gross domestic product (GDP) on average compared to around 8.7% in high-income countries during 2015.2 Nevertheless, public pension expenditure in the region is expected to increase progressively during the next few years. It is projected that between 2020 and 2100, the increase in the dependent population in Latin America will be unprecedented. As a result, Latin America will be the worldwide region with the highest share of elderly population (32%) by 2100.[1,4]

Most of Latin American countries have unfunded defined-benefit pension systems, also known as pay-as-you-go (PAYG) pension systems, where workers pay for the pensions of current pensioners and government contributes with certain percentage of pension benefits.[1] PAYG systems are expected to experience higher increases in their pension expenditure as the population ages. Therefore, a higher demand may result in financing gaps if the workers' contributions are insufficient and then long-term reforms may be needed. Countries with funded defined-contribution systems (where pension benefits depend on the contributions and financial returns are based on individual contributions) may experience lower increases in public pension expenditures.[1] However, lower increases in public pension spending may be associated with low levels of coverage for older population.[1]

According to the 2030 agenda for sustainable development published by the United Nations Development Program, aging and older populations can be part of a sustainable development.[5] In order to achieve this, countries must make proper decisions based on policies that promote and include older people and their agency as a solution to upcoming development challenges. For pension systems in Latin America, raising retirement ages and contribution rates, especially in countries where those are relatively low, may help to build temporary buffers to afford future increases in pension expenditures associated with aging.[1]

Population aging is challenging not only for the fiscal sustainability of public pension but also for healthcare systems in the region.

COSTLIER HEALTHCARE SYSTEMS

An older population increases the demands for the health system.[6] Not only is the number of people who contact the health system greater but also the number of annual contacts, hospitalizations, and the average length of stay at the hospital are higher.[3] Currently, the average of public health expenditures in Latin America is 4.4% of GDP. Given this starting point, in the absence of healthcare system reform, Latin America is projected to experience the largest increase in health expenditures compared with any region worldwide over the next 80 years.[2] To address this demographic change and manage health spending growth, while providing adequate and opportune health services to population, Latin American health policies will have to embark on efforts and efficiency-enhancing reforms not only to increase coverage and sustain it over time but also to reduce inequities and facilitate access to health systems—especially in elderly populations with vulnerabilities.

RESEARCH OPPORTUNITIES IN LATIN AMERICA REGION

A population's health cannot be understood without an understanding of their healthcare system and their country's economic situation. Having this on account, longitudinal health and retirement studies (HRS) have been established recently to provide a reliable resource for data on the health and economic circumstances associated with aging at individual and population levels.[7] These studies aim to create nationally representative sample sizes of between 10,000 and 20,000 people, not only to increase the understanding of aging but also to provide scientific data for policy changes and to develop public policies.[2,7] However, in the Latin America region, most studies are not

structured or designed to measure these elements and their interactions. Many countries around the world already have recognized the relevance of multidisciplinary, longitudinal HRS-type surveys.[2] Mexico was the first country in Latin America to adopt these (in 2002). HRS are also now underway in Brazil and Costa Rica but so far no other Latin American countries have incorporated these surveys, so they remain an opportunity for future research.[2]

During the next few years, policy makers and academia may advocate for improvement in statistical systems and conduct not only population-based studies but also health economics studies to provide the needed evidence to gradually reform pension and healthcare systems in Latin America. These measures can help to lessen the impact of aging on health systems while preserving adequate access to healthcare services and pension benefits.

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Drug Disinvestment–Is It Needed and How Could It Work?

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Despite being conceptually appealing from an HTA perspective, disinvestment schemes have proven to be challenging for local payers to implement and realize savings. An alternative disinvestment model may be more appealing: temporarily reimbursing new treatments where evidence is available, following by funding, discounting, or disinvesting

As public healthcare budgets face increasing constraints, new health technologies face increasing evidentiary hurdles to justify investment of limited public economic resources. Several emerging classes of therapies, including chimeric antigen receptor-T cell (CAR-T cell) and gene therapies, offer transformational, potentially curative patient benefits in areas of significant unmet need and often in rare patient populations. As such, they can demonstrate positive benefit-risk ratios to regulators at earlier stages of their clinical development, when supported by less mature and comprehensive data packages. However, reflective of their transformational patient benefits, these therapies can be cost-effective at very high per patient prices.

The Institute for Clinical and Economic Review recently issued reporting, pricing Zolgensma (onasemnogene abeparvovec-xioi), a gene therapy for spinal muscular atrophy, at nearly $1.5 million per treatment using a cost per QALY gained threshold.[1] Affordability of these newer, higher-value potentially curative therapies could be better supported with disinvestment schemes that remove funding for certain low-value healthcare interventions with poor evidence of clinical effectiveness, and/or replace high-cost medicines with lower-cost alternatives with comparable efficacy, such as generics and biosimilars. However, despite being conceptually appealing, previous disinvestment attempts have faced significant challenges in their implementation. This article discusses why this is the case, whether there is a need for disinvestment, and how this could potentially work.

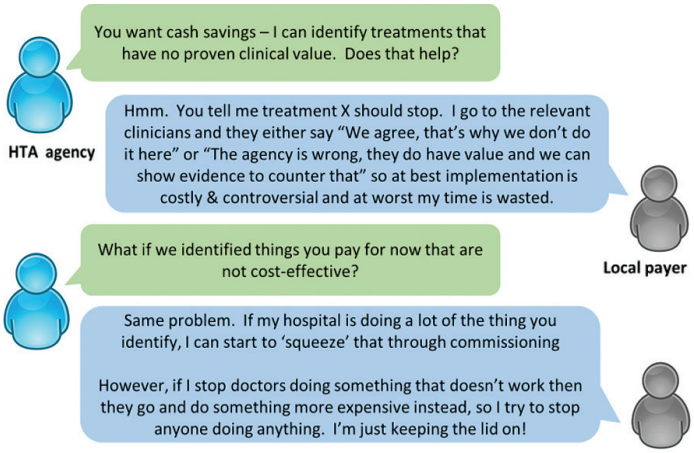
KEY CHALLENGE #1: DEFINING VALUE

Health technology agency (HTA) bodies such as the National Institute for Health and Care Excellence (NICE) and the Scottish Medicines Consortium issue recommendations for public reimbursement of new healthcare technologies based on their incremental clinical- and cost-effectiveness. However, they do not directly influence local services, nor do they have budgetary responsibilities. Thus, implementing this guidance can be very challenging for local payers who are frequently facing significant financial constraints and for whom modelled future cost savings (especially considering when these will occur and with what degree of certainty) may not be a priority given their current budget situation. As a result, the value of investing or disinvesting in certain therapeutics may look very different to a local payer than to an HTA body.

In cases where a new lower-cost medicine replaces an existing medicine with a similar clinical profile, disinvestment is of high value to a local payer. An example of this is, disinvesting in branded products with generic or biosimilar alternatives. However, while a new medicine may appear to be cost saving from an HTA perspective by reducing future hospitalizations and other costly interventions, they are often not perceived as such from the view of a local payer. For example, new hepatitis C virus therapies have curative potential and may avert the need for liver transplants and drastically reduce liver cancer rates, but payers however may not realize these cost savings to their budget for many years after initial treatment and such therapies demand a large upfront investment. Similarly, novel oral anticoagulants may be deemed cost-effective from an HTA point of view, including facilitating disinvestment in warfarin monitoring clinics. But for a local payer, this reduction in monitoring services may have little impact on their overall budgetary spend if costs such as how much staff capacity can be reduced are not considered (most staff are on long-term employment contracts and are considered a fixed cost). Further, HTA bodies do not consider the true value of resources freed; local payers may not value releasing dermatology time but strongly value gaining intensive care time.

It is apparent that while HTA bodies may provide value as gatekeepers to help manage the costs of healthcare technologies, their investment

Figure 1. Discrepancy between HTA body and local payer viewpoints



recommendations may not be aligned to local budget holders' priorities at the frontline of healthcare delivery. Similarly, disinvestment decisions issued by HTA bodies also may not always consider the costs of redeploying resources that might otherwise bring meaningful value to a local payer and the true value of resources freed.

KEY CHALLENGE #2: IMPLEMENTATION CHALLENGES

Even when local payers and HTA bodies agree on what is considered a low-value treatment, there may be substantial challenges implementing disinvestment recommendations. If clinicians agree with such a recommendation, then they will likely not be prescribing that therapy. However, clinicians may oppose moves to preclude access for therapies for which they have direct experience of their benefits for certain patients. Even if they concurred, they may use higher-cost alternatives in its place. We illustrate this situation in an imaginary dialogue between an HTA body and a local payer (Figure 1).

While the actual dialogue may differ in the real world, in reality, cost savings from disinvestment efforts that may seem clear and evidence-based to an HTA body may in fact be nebulous and difficult to implement to a local payer. Examples of disinvestment where funding is removed for older healthcare interventions with a lack of strong evidence supporting their effectiveness tend to be less controversial. For instance, in November 2018, the NHS England announced that they will no longer fund a variety of low-value interventions, including silk garments and bath oils on which they currently spend £17 million a year.[2] However, many other previous disinvestment attempts have faced some major challenges in their implementation, particularly those reversing prior reimbursement decisions.

Conditional financing in the Netherlands was designed to be a scheme whereby orphan medicines undergo economic re-evaluation 4 years post-launch. After the first few medicines were found not to be cost-effective under this process, the draft reports resulted in public and clinician outcry.[3] Consequently, the medicines were never de-listed nor were their prices reduced. In another example, NICE attempted to revisit the recommendation of erlotinib in 2014, having initially approved the therapy in an all-comers population for pretreated lung cancer in 2008. This followed a phase 3 trial in patients who were EGFR mutation-negative that showed the generic drug docetaxel was more effective at prolonging survival than erlotinib. However, after the first appraisal consultation document restricted reimbursement of erlotinib in EGFR mutation negative patients in February 2014, there was substantial physician and patient pushback,[4] including concerns that the toxicities of docetaxel precluded it as an option for many patients. Two further committee meetings were held before final guidance reinstated restrictions in August 2014.

OR MAYBE WE NEED TO LOOK AT DISINVESTMENT IN A DIFFERENT WAY?

Disinvestment is clearly conceptually appealing but faces major challenges in its implementation that may outweigh any potential benefits. Alternatively, we may consider another disinvestment model: temporarily reimbursing innovative new technologies until more evidence is generated and then funding, demanding discounts, or disinvesting when we have a clearer idea of their clinical benefits. The newly reformed Cancer Drugs Fund (CDF) in England has enabled such a model since 2016, within which the CAR-T cell therapy Kymriah (tisagenlecleucel) was recommended for funding 10 days after European market authorization. But even this may face major challenges. If therapies are disinvested because their price is not justified by the subsequent evidence, there may be equity issues, such as introducing a time lottery whereby patients diagnosed after a certain date will not be able to access potential groundbreaking therapies. However, as of September 2019, no therapy has entered the new CDF and not subsequently been recommended by NICE. This will be the true test of this model—until then the jury is out!

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ADDITIONAL INFORMATION

The preceding article was based on an Issues Panel presented at ISPOR Europe 2018. To view additional presentations from this meeting, go to https://www.ispor.org/conferences-education/conferences/past-conferences/europe-2018/conference-presentations.

Novel Value Measures and European HTA: Implications for Pharma/Device HEOR

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We must recognize that the term "value" may be more appropriately thought of as "benefit" which, in turn, triggers a discussion on the opportunity cost of other forgone benefits. New cost-effectiveness modeling methods are required to accommodate the novel sources of value.

MOVING BEYOND THE QALY

The recent ISPOR Special Task Force on U.S. Value Frameworks[1] identified 12 value elements for healthcare innovation. With the quality-adjusted life year (QALY) as the starting point and adding accepted sources of value (such as cost savings, productivity, and the adherence-improving factor), Lakdawalla et al suggested several more novel, uncertainty-related sources, such as the value of hope, option value, and the value of knowing. Informally referred to as the *"Value Flower,"* this offers an interesting starting point to consider how novel sources of value may apply to European health technology assessment (HTA).

There appears to be broad support for a wider perspective on value. For example, an informal audience poll (N~300) at the start of the ISPOR-EU 2018 panel discussion, "Do Novel Value Measures Have a Place in European HTA?" (Breakout #2, IP6) revealed that around three-quarters of respondents thought that the QALY inadequately captures the patient benefit and should be supplemented by other measures of value, and that the views of non-patients (also receiving benefits from the same payer) who may not receive the benefit of a new innovation — but will share the cost — should be included in HTA.

NOVEL VALUE MEASURES AND EUROPEAN HTA: KEY ISSUES UNDER DEBATE

From an HTA perspective, the inclusion of novel sources of value raises several issues:

Are we using the correct terminology?
– The much-used term "value" often conveys the benefits that a health technology offers, but in any collectively funded healthcare system, the term might more appropriately mean, "Do the benefits of a new intervention outweigh the opportunity cost?." So whatever gets included in the benefit function, eg, a concern for inequality in health as well as health gain itself, these need to be reflected in what the system doesn't fund as well as in the new investments in drugs and other interventions.

Who has the right to define benefit and how inclusive should this be?
For example, how do we differentiate direct medical care from care that supports the activities of daily living to promote independence, well-being from social interaction, and knowing versus just being informed? In simple terms, does the "Value Flower" require more petals?

Are novel benefits finite or infinite?
This provocative question addresses whether the benefits of a drug are finite, with each new study articulating different elements of a single, all-encompassing QALY or whether value elements X, Y, and Z are indeed incremental to the foundational QALY.

Do current CE modeling techniques accommodate novel benefits?
Acknowledging the foundational standing of the cost-per-QALY metric (also known as "cost-utility analysis") in HTA, is there a place to expand this to add the other elements of value as well as broaden the methods via such tools as multicriteria decision analysis? There is literature showing how this can be done – for example, distributional or augmented cost-effectiveness analysis.[2] However, there is a need for a wider discussion on other possible aspects of the benefits to include.

How do we reconcile "proof versus promise" for a health technology?
While the dynamic nature of a treatment's cost-effectiveness has been suggested,[3-4] a more fundamental tension faces society and HTA bodies in particular: "Given the resources available, do we invest in a new treatment with unproven effectiveness or continue to spend on existing, tried-and-tested treatments that have been on the market for a long time?" And, if the latter is chosen, what long-term societal benefits will be foregone if the scientific community does not continue to advance medical science that may find a future cure? The ISPOR Special Task Force labelled this element of value "scientific spillovers." Linked to this is the challenge of generating sufficient evidence to justify investment and establishing an iterative framework to determine how

much a system should pay for a product at launch, assessing whether additional evidence should be generated postlaunch, how this is incentivized and funded, and how the product's price can be adjusted as new evidence emerges.[5-6]

NOVEL VALUE MEASURES AND EUROPEAN HTA: IMPLICATIONS FOR PHARMA/DEVICE HEOR

Three implications are worth consideration by the HEOR researcher embedded within a pharmaceutical or medical device setting:

1. The commercial application of expanding a product's benefit profile – Within an existing treatment indication, recognize that emerging evidence on a new or existing benefit secures the drug's place in therapy and from a commercial perspective, may drive uptake and market share. In markets that allow a price increase, new trial or real-world data may help support a price adjustment.

2. Opportunity cost – In all collectively funded healthcare systems, consider describing the average foregone treatment opportunity and its associated benefits; ie, the things that a payer will not be able to do for the same amount of money. In simple terms, what unmet needs will be addressed and what are examples of unmet needs that will not be met? While acknowledging that the needs of the sick should not be ignored, preparing to debate the opportunity cost issue will focus the innovator on truly capturing the unmet need that is being addressed. Literature showing how opportunity costs can be estimated empirically is now emerging, with evidence from the United Kingdom, Sweden, Australia, and others.[7]

3. Capturing the value of disruptive innovation – In markets where access and reimbursement are driven by HTA relying on the cost per QALY, there is potential to mitigate this by demonstrating the product's other benefits (ie, elements of value) as long as the same aspects of value are assessed in measuring the opportunity costs.

...the current HTA approach was developed in an era when the focus was on high-prevalence, chronic diseases, it is now being applied in the era of precision medicine.

EMBRACING INNOVATION IN AN HTA WORLD

From an innovator's perspective, one could argue that while the current HTA approach was developed in an era when the focus was on high-prevalence, chronic diseases, it is now being applied in the era of precision medicine. Thus the cost-per-QALY approach presents limitations for some of the transformative treatments now in development such as curative gene therapies and highly anticipated treatments that society wants in the future, for example, in autism and Alzheimer's disease.

Alternatively, from an HTA perspective, perhaps the current critical issues are less around the methodological considerations that comprise an HTA, but instead about addressing the resource constraints facing collectively funded healthcare systems: (1) such public systems are limited in their ability to raise prices, (2) the supply of new health technologies, and (3) adoption of any new health technology in one deserving area of medical care implies less funding available for other services. Furthermore, although this is less explicit, the challenge of "opportunity cost" is central to resource allocation decisions in all healthcare systems funded collectively, with fixed budgets or not. Thus, the key point is that the focus of debate is usually about the merits of the new technology and rarely about the forgone benefits associated with alternative uses of resources; that is, we need societies to become more transparent and open about the opportunity cost of adopting innovation.

The insights for the pharma and device HEOR scientists are of real, practical use: (1) recognize the ongoing value of generating new real-world effectiveness evidence as the basis for describing the benefits to different patient groups and supporting a product's price; (2) be prepared to discuss the opportunity cost for adopting your treatment innovation versus maintaining the status quo; and (3) develop evidence of value beyond the QALY argument.

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ADDITIONAL INFORMATION

The preceeding article is based on am issue panel given at ISPOR Europe 2018. To view the presentations, go to https://www.ispor.org/conferences-education/conferences/past-conferences/europe-2018/conference-presentations.

A Collaborative Approach to the Intersection of the Real World With the Highest Quality Standards

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The 21st Century Cures Act calls for real-world evidence to help support regulatory decision making. A collaborative community model can help this cause by bringing together multiple stakeholders, including academic thought leaders, regulatory bodies, pharmaceutical industry partners, and patient advocacy groups around a real-world, shared, deeply detailed, high-quality data set.

Immediately following the initial approval of medications, there is frequently a gap between the information generated from phase 3 clinical trials and their optimal use in usual clinical practice. The 21st Century Cures Act was adopted in 2016 with the goal of encouraging innovation in clinical trials and accelerating drug development. One important aspect of the 21st Century Cures Act required the US Food and Drug Administration (FDA) "to evaluate the potential use of real-world evidence to help to support the approval of a new indication for a drug… [and] to help support or satisfy post-approval study requirements."[1] Thus, the FDA has organized efforts to understand and develop guidance on the use of real-world evidence (RWE) to enhance the understanding of marketed drugs. RWE has been defined as healthcare data from a variety of sources outside of clinical research. In this list of sources, FDA includes "electronic health records (EHRs), claims and billing data, product and disease registries, and data gathered through personal devices and health applications."[2] When the quality of RWE is high, multiple stakeholders can benefit.

Although clinical trial data are perceived as the gold standard, the intersection between data from clinical research and usual clinical practice that maintains the highest level of quality has tremendous promise for complementing standard clinical trials, advancing the regulatory process, and improving patient care.

These stakeholders can interpret and collaborate on collections of RWE and bring important perspectives to the dataset. This group may include academic thought leaders, regulatory bodies, pharmaceutical industry partners, patient advocacy groups, and payers. As the utility and use of high-quality RWE continues to evolve, a multistakeholder approach to research holds great promise.

To illustrate this collaborative approach, this manuscript will walk through an example within a turnkey primary biliary cholangitis (PBC) real-world evidence community, a study of participants with PBC. PBC is a rare, chronic, cholestatic liver disease that may progress to cirrhosis if left untreated. These patients are at risk for developing clinical events, including complications of portal hypertension, hepatocellular carcinoma, liver transplantation, and death. First-line therapy for PBC is ursodeoxycholic acid (UDCA). Unfortunately, approximately 1 out of 4 patients do not have sufficient response to UDCA. Obeticholic acid (OCA), the first new agent approved in decades for the treatment of PBC, provides an additional option for those with an inadequate response to UDCA alone. The PBC collaborative community mentioned above has over 500 participants in the United States and captures real-world insights on OCA use, effectiveness, and adverse events in a wide variety of patients taking OCA. The top academic thought leaders in PBC designed the protocol and continue to direct study decisions with regulatory input. Partners include those from industry and from the PBCers, a patient advocacy group.

In light of recent reports of improper prescribing practices, patients with moderate-to-severe liver disease enrolled in this study have been of particular interest. The FDA-approved label recommends an OCA starting dose of 5 mg daily with titration to a maximum dose of 10 mg daily for noncirrhotic and early stage cirrhotic patients. However, the label specifies that clinicians should limit the starting dose to 5 mg weekly in patients with moderate-to-severe liver impairment with titration to a maximum of 10 mg twice per week.

In a news release prompted by reports of serious adverse events connected to OCA through the FDA Adverse Events Reporting System (FAERS), the FDA announced that some clinicians were prescribing the standard dose to patients with moderate-to-severe liver impairment, rather than the adjusted dose. In several of the reported cases, patients with moderate-to-severe liver impairment incorrectly received daily dosing of OCA. Ultimately, the FDA added a boxed warning and dosing table to the OCA package insert and an informational medication guide for patients. Longitudinal follow-up of patients in this PBC cohort has and will continue to provide long-term safety and effectiveness data in a diverse population of patients with mild and advanced liver disease being treated with OCA. The concerns, input, and actions of multiple stakeholders have already helped to shape its ideal use.

As RWE gains traction in the regulatory realm, high-quality, academically backed sources will become increasingly important. By definition, patients in the real world include those of all backgrounds and with the entire spectrum of disease severity; there is "renewed interest in the use of real-world data [RWD] to... bridge the evidentiary gap between clinical research and practice."[3] Although clinical trial data are perceived as the gold standard, the intersection between data from clinical research and usual clinical practice that maintains the highest level of quality has tremendous promise for complementing standard clinical trials, advancing the regulatory process, and improving patient care. It takes the convergence of a collaborative group of stakeholders around these data to truly illuminate their potential.

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ADDITIONAL INFORMATION

For further articles on the 21st Century Cures Act, you may refer to the November/December 2018 issue of Value & Outcomes Spotlight, available at https://www.ispor.org/publications/journals/value-outcomes-spotlight

Q&A

Aging in Asia: A Japanese Perspective
An Interview With Isao Kamae, PhD, MD

Value & Outcomes Spotlight had the pleasure to sit down with Isao Kamae, PhD, MD, to discuss aging in the global population, with special emphasis on Japan. An active contributor to ISPOR for many years, Isao is a professor of health technology assessment (HTA) project, Graduate School of Public Policy, The University of Tokyo, Japan. He also serves as a research director, The Canon Institute for Global Studies, Tokyo and an advisory expert for WHO and OECD. He has previously worked as an associate professor at Shimane Medical University from 1993 to 1994 and Kyoto University Hospital from 1994 to 1997 and as a professor at Kobe University School of Medicine from 1997 to 2007 and Keio University from 2007 to 2012. His research interest is primarily in health economics and HTA. He has published 180 papers and completed work on 31 books. He serves as an editorial board member for *Value in Health Regional Issues* and *Journal of Medical Economics* and was the first Asia-origin member of the ISPOR Board of Directors from 2004 to 2006.

Value & Outcomes Spotlight: **Global demographic statistics show an aging of the population in many countries, but this is particularly an issue for Asian countries like Japan, isn't it?**

Kamae: Yes. The UN World Population Prospect: The 2015 Revision reports the proportion of the population over 65 years old to the whole population in the world was 7.7% in developed and 3.8% in developing countries in 1950. But these percentages grew to 17.6% and 6.4%, respectively, in 2015, and are projected to reach 27.4% and 16.8%, respectively, in 2060. So, this is indeed a global problem, particularly for developed countries.
But in Asia, the statistics are even more extreme. According to the Databook of International Labor Statistics from the Japan Institute for Labor Policy and Training 2017, the 3 regions with the largest proportion of elderly persons in 2015 were Japan at 26.3%, Hong Kong at 15.1% (9.6% in China), and South Korea at 13.1%. These are projected to rise to 36.3% in Japan, 35.1% in South Korea, and 34.5% in Hong Kong (27.6% in China) by 2050.

What are the consequences of the aging of the population? What do you see happening in Japan?

Three challenges we are seeing already and only expect to worsen: first, a shortage of labor power, as more of the population enters retirement; second, an increase of diseases that more commonly have adult onset, such as central nervous system disorders like Alzheimer's disease and certain cancers; and third, a growing financial burden of elderly healthcare.

Making matters worse, in Japan, the aging of the population has coincided with a declining birthrate. It implies that the ratio of elderly versus working-age population has been changing rapidly. The Japanese statistics report that the ratio of the population over 65 years versus those between ages 20 to 64 years was 1.0/5.1 in 1990 but will be 1.0/1.8 in 2025 and 1.0/1.2 in 2060. The trends of declining working-age population will force Japan to rely on more imported labor.

Japan faces the changes in disease structure; that is, increase of adult diseases accompanied by progression of aging, especially the increasing prevalence of dementia and growing need for community-based care. The number of dementia patients was 4.62 million (15% of the population over 65 years old) in 2012 and is projected to reach up to 7 million (20%) in 2025.
The elderly are a key cost driver of medical expenditures, which amount to JPY942,000 per capita for patients over 75 years old belonging to the national elderly health insurance. The estimate is about 6 times as large as that of the population under 75 years old having employees' health insurance, ie, JPY167,000 per capita. The higher expenditures for elderly patients can be attributed to generally poorer health status and their demand for innovative (and expensive) medical technologies.

Why is Japan concerned about the consequences caused by the aging of population, and how has Japan been finding solutions?

The aging of population seriously threatens the affordability and sustainability of universal health coverage (UHC) in Japan. Japan has an urgent need for healthcare reforms to maintain the affordability and sustainability of UHC.

The reforms must be accomplished at both macro and micro levels of the current healthcare system. There are 3 major challenges for healthcare reforms at the macro level: first, shift from hospital-based interventions to community-based preventive and primary care; second, priority setting in chronic diseases relevant to aging such as dementia, cancer and so on, rather than acute diseases; and third, capacity building for long-term insurance and facilities for elderly care.

What are some important developments in HTA in Japan, and how will such developments have an impact on the aging society?

After 3-year provisional implementation from 2016 to 2018, in April 2019, the Japanese Ministry of Health, Labor and Welfare institutionalized a new HTA policy as a micro-level reform, requiring cost-effectiveness analysis for selected drugs and medical devices. It is the first case in the world of performing an "ICER-based" price adjustment.

The new HTA policy will become a trigger to expand the concept and methods of value assessment in healthcare in aging society of Japan. The lessons Japan experiences will be useful globally for other countries, too.

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