Artificial Intelligence:
THE KEY TO UNLOCKING REAL-WORLD DATA?

ALSO:
An Interview With Eric Topol, MD

How Dynamic Visualizations
Are Changing the Way We Understand and Communicate HEOR Findings
What if you could use curated registries to rapidly:

- Understand treatment and prescribing patterns
- Identify ideal patients for new treatments
- Compare & predict treatment outcomes across different populations

Millions of patients. Billions of data points and outcomes. Find out how our curated registries can change your likelihood of success.

WWW.OM1.COM
## TABLE OF CONTENTS

### FROM THE EDITOR
4  The Artificial Intelligence Issue

### ISPOR CENTRAL
5  ISPOR Speaks  
   Getting the Right Science
8  HEOR News
10  Conferences & Education
14  From the Journals

### FEATURE
16  Artificial Intelligence: The Key to Unlocking Novel Real-World Data?
21  By the Numbers: Artificial Intelligence in Health—Trial and Tribulations

### HEOR ARTICLES
22  Is Artificial Intelligence the Next Big Thing in Health Economics and Outcomes Research?
25  A Health Economist Walks Into a Tech Company: Principles for Reproducible Real-World Analyses
27  Truly, Broadly, and Deeply: How Dynamic Visualizations Are Changing the Way We Understand and Communicate HEOR Findings

### Q & A
31  Artificial Intelligence in Health—An Interview with Eric Topol, MD

---

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

A few years back, I read with great interest The Patient Will See You Now: The Future of Medicine is In your Hands, in which the author, Eric Topol MD, described how digital health and connected devices will combine to turn the traditional paternalistic doctor-patient relationship on its head and give rise to a new era of patient centricity in healthcare. Whether or not we’ve observed the kind of disruption he predicted for doctor-patient encounters can be debated, but there can be little doubt that efforts have intensified to ensure that the voice of the patient is heard.

Dr. Topol’s current book, Deep Medicine: How Artificial Intelligence Can Make Healthcare Human Again, was only published this March so many of us have probably not yet had the opportunity to read it. In the meantime, this issue of Value & Outcomes Spotlight focuses on the theme of artificial intelligence (AI) in healthcare, including a feature article on the ability of machine learning and natural language processing (NLP) to unlock the full potential of real world data, another contribution that asks the provocative question of whether AI will be the next big thing in HEOR, a by-the-numbers infographic page on the trials & tribulations of AI in healthcare (courtesy of the ISPOR Student Network), and, to cap it all off, a Q&A with Dr. Topol himself.

Our ISPOR Central section contains an article by Chief Science Officer Dick Willke, in which he ponders some big questions, including the purpose of his existence (as ISPOR CSO, that is) and the process by which ISPOR prioritizes certain scientific themes in the HEOR realm. Also, he recapitulates the inner workings of the abstract review and acceptance process, describing the various layers of review, scoring, and eventual assembly of the ISPOR conference program. A close read could yield insights on how to improve your abstract submissions and increase chances of acceptance—might be interesting to apply some NLP to see what pops out.

Finally, this issue includes two additional articles related to our ‘techy’ theme. The first offers guidance on the development of re-usable programming code in analyses of real-world data. Reproducibility of analytic results is key to instilling confidence in the validity of a database analysis, but how can this be achieved when the actual programming code is usually not available or is inscrutable when it is? Lessons from software engineers, described by the authors, might help in this regard. The second piece describes dynamic data visualization approaches for more impactful reporting of HEOR results, including database analyses, modeling studies, and network meta-analysis. Newly available data visualization software is ushering in a new paradigm for distilling analytic insights, promoting interactivity on the part of consumers of the data.

It doesn’t take much intelligence—artificial or human—to predict that this issue of Value & Outcomes Spotlight will hold your interest.

Enjoy!

David Thompson, PhD
Editor-in-Chief,
Value & Outcomes Spotlight
Getting the Right Science

Richard Willke, PhD, ISPOR Chief Science Officer

Have you ever wondered how our conference themes, plenaries, and sessions are determined? Does ISPOR have a scientific agenda per se, and if it does, who determines it? (And what does a Chief Science Officer really do—when he’s not fiddling with his tricorder, that is?) In any scientific gathering, while getting the science right is critical, getting the “right” science may be equally important.

Fundamentally, ISPOR relies on member input for what is selected and presented under its banner. This approach is consistent with the concept of “emergence” (or “emergent order”) or “self-organization” in complex systems, or the “invisible hand” in economics. No single person makes the rules, determines the outcomes, or decides on prices or resource allocation—these result from the natural forces within the system and from the actions of all its “components.” Not to let our own members and environment drive what ISPOR does would be foolish and ultimately unsuccessful. One of my favorite quotes from Friedrich Hayek makes this point quite nicely for my own profession: “The curious task of economics is to demonstrate to men how little they really know about what they imagine they can design.” Another famous person put it more simply: “Life will find a way.”

OK, that’s great in theory, you say—but someone, somehow, must put together a conference program. How does this really happen?

First, I’ll mention a couple of recently developed, systematic intelligence sources on topics that generate the most interest. One is our Top 10 HEOR Trends membership survey, published last year for 2018 and this past January for 2019 (available at http://www.ispor.org/top10trends). ISPOR content and conference themes are also determined through the input of many including the Board of Directors, ISPOR Councils, Committees, Special Interest Groups, Task Forces and even Chapters. Other member and audience surveys are also important sources of input. Finally, one of our most senior and representative advisory bodies, the Health Science Policy Council, helps to formulate not only the Top 10 survey, but provides comment on major ISPOR themes.

For each major conference, program formation begins with the selection of 3 program co-chairs, starting roughly a year before the conference is to take place. This selection is led by a team including our CEO, Nancy Berg, the ISPOR President-elect and other senior members and staff. Conference co-chairs are selected for their expertise with important consideration to stakeholder representation as well as diversity such as gender, country, age, and so on. Co-chairs are ideally prominent members of our profession and the broader healthcare world, with a combination of scientific, policy, and international expertise, who then help us shape the conference theme and plenaries for their invited meeting.

Perhaps of more interest to many of you is how workshop, issue panel, and research podium selection decisions are made. First, of course, you must submit your abstracts; your collective submission decisions form the topical base for the program. In consultation with the conference co-chairs, ISPOR then invites 3-4 members as co-chairs to lead the acceptance decision process for each type of session (ie, there are 3 workshop review co-chairs, 3 issue panel review co-chairs, and 4 research podium co-chairs). Again, these invitations are extended with consideration to country representation, gender and other areas of diversity. Next, over 500 volunteer reviewers are recruited to read and rate the abstracts. They each rate about 20 abstracts in one session type, giving each one scores on various criteria that result in a summary score between 5 (best) to 1 (worst). Each workshop and issue panel abstract submission are typically rated by 8 to 10 reviewers, while research abstracts are rated by 4 to 5 reviewers. The mean of the reviewers’ scores is the primary determinant of whether of a given abstract gets chosen for the program. However, considered statistically, the mean score has a standard error of around 0.25 when there are 10 reviewers (based on a sample of scores I reviewed), so small differences in means can be based on random differences across reviewers.

Given the typical number of issue panel and workshop submissions versus program slots available, about 20% to 30% of those submissions can be accepted. For each type of session, the session review co-chairs and a team of qualified ISPOR staff collaborate to discuss and agree on the submissions. Their decisions are based on the reviewer ratings as well as other...
strategic considerations such as the panel representativeness (eg, issue panels need to include stakeholders, appropriately), audience participation, and overall priority and diversity of topics. While the top 10- to 15%-rated abstracts generally are selected, due to the sampling variability in scores, we do not apply an exact cutoff for acceptance based on ratings alone; that’s where those other factors come into play more heavily. Inevitably, some very good abstracts do not get accepted; sometimes we encourage those submitters to resubmit a similar session for the next conference.

Selecting the research abstracts is a bit more complicated process because they not only have to be judged for acceptance as oral podium presentations (versus posters) but also must be grouped into cohesive sessions of 4. First the research cochairs select a probable set of session topics, based mainly on the number of submissions by broad topic category. They then select abstracts into appropriate session topic groupings; again, their selections are based heavily on reviewer ratings, but they apply some of their own judgment (essentially as additional reviewers) to help make final decisions. ISPOR staff play very little role here except to manage the process (which our Meetings-Program team does exceptionally well, I must say).

Out of roughly 2000 research abstract submissions, 60 to 80 get selected for oral podium presentations. Most of the remaining abstracts are selected for poster presentations, although we do carefully review the lowest tier of ratings for general acceptability; only 5% to 10% are not accepted as either podium or poster presentations, thus providing opportunities for many researchers at all levels to present their work at our conferences.

ISPOR Chapters, Special Interest, and other group work also compete for valuable session time. These member-generated group proposals are reviewed by a senior staff team and selected based on relevance and timeliness of topic.

ISPOR strives to serve as a well-functioning platform for our members’ ideas and health economics and outcomes research (HEOR) in general. Member volunteers steer the extensive peer-review process and as in any endeavor, work is more innovative and engaging when more are involved. We truly value all your contributions as submitters, reviewers, attendees, and speakers. See you in New Orleans, Bogota, or Copenhagen!
Unwrapping HEOR

For more than 20 years, readers have relied on Value in Health to deliver high-quality, scholarly articles that advance the field of health economics and outcomes research (HEOR). Each issue contains peer-reviewed, original research, and health policy articles that help healthcare leaders make evidence-based decisions that have a real-world impact on global populations and healthcare systems.

Later this year, the journal will unveil a new look for the publication—one that reflects the level of sophistication and prominence of the role HEOR is currently playing in improving healthcare decisions. Bold new look—same trusted content.

*Value in Health*... unwrapping the science of HEOR for readers around the world.

www.ispor.org

505 Lawrence Square Blvd South, Lawrenceville, NJ 08648
© ISPOR – The professional society for health economics and outcomes research
1. Lilly to Introduce Lower-Priced Insulin (Eli Lilly & Co.)

In response to criticisms over the prices of its insulins in the United States, Eli Lilly & Co. announced in March that it would be introducing an authorized generic for its product, Humalog (insulin lispro injection 100 units/mL), that would sell for about half the list price of Humalog. “The significant rebates we pay on insulins do not directly benefit all patients. This needs to change,” said David A. Ricks, Lilly’s chairman and CEO. “There are numerous ideas, including the rebate reform proposal from HHS. For people with diabetes, a lower-priced insulin can serve as a bridge that addresses gaps in the system until a more sustainable model is achieved.”


2. Pharmacare Advisory Council Calls for National Drug Agency, but No Guidance Yet on Universal Coverage (CBC)

An interim report from the Canadian Liberal government’s advisory council calls for the creation of a new national “arm’s length” agency to manage prescription medications, including negotiating prices and creating a formulary of approved, covered drugs. But the interim report did not provide guidance on how the federal government should ensure that all Canadians have access to prescription drug coverage — notably whether it should adopt a universal, single-payer pharmacare plan, or whether it would simply fill the gaps for those who don’t have coverage under other insurance plans.


3. Can Roche’s Little Tech Startup Help the FDA Change Clinical Trials? (STAT News)

Forbes’ Matthew Herper talks about Flatiron Health, a small New York startup that was recently acquired by Roche, which is trying to use real-world data from patients’ electronic medical records to replace more traditional clinical trial data. In March, Flatiron renewed and expanded its research relationship with the FDA. On the prospect of perhaps replacing control groups one day with real-world evidence, FDA has expressed caution, saying this is an idea that it is “still exploring.”


4. Next Phase in Effective Cost Control in Health Care (JAMA)

Dr Ezekiel J. Emanuel, Aaron Glickman, and Sarah S.P. Dimagno in the March 7 Viewpoint column say although total US healthcare costs in 2017 were almost $650 billion less than anticipated, the cost of healthcare remains a significant financial and emotional strain. They recommend that the United States must do more about controlling drug prices, set national and state-level benchmarks for total healthcare cost growth that are linked to economic growth and population aging, expand the adoption of alternative payment models in the private market, and wield antitrust powers to address hospital consolidation with other hospitals and through purchasing of physician groups.

https://jamanetwork.com/journals/jama/fullarticle/2728102?utm_source=NPC+Contact+List&utm_campaign=05ba1eb39b-EMAIL_CAMPAIGN_2019_03_07_07_33_COPY_01&utm_medium=email&utm_term=0_3ddd3927eb-05ba1eb39b-198287949

5. Drug Charges in Scotland: The Impact of Free Prescriptions (Valid Insights Blog)

Writing at the consultancy’s blog, James Wright reviews how free prescriptions have affected dispensing rates and patient health in Scotland. From 2006-2007 — when free prescriptions were introduced — to 2015-2016, the number of prescriptions dispensed went from just under 80 million to just over 100 million.


6. FDA Releases New Draft Guidance on Steps for Naming of Biological Medicines (FDA)

In part of an effort to encourage biosimilar competition in the United States, FDA has released an updated draft guidance, “Nonproprietary Naming of Biological Products: Update” on the naming of branded biologicals and interchangeable biosimilars. “We’re fully committed to the suite of announced and upcoming policies to help advance the goal of a robust, high-quality, competitive market for biosimilar products. But I do not believe that the naming convention should be used to advance these goals if it could come at the expense of the ability to ensure patient safety,” said FDA Commissioner Scott Gottlieb in a statement. “Nor do I believe the inclusion of a suffix will frustrate the broader aim of inspiring strong biosimilar competition.”

7 Combating Cancer With “Cost-Effective” Strategies (CEVR)
Xue Feng, PhD, a postdoctoral fellow, blogs at the Center for the Evaluation of Value and Risk in Health about the increasing burden of the cost of cancer treatment in lower-middle income countries (LMIC). Despite this burden, only 3.4% of published cost/disability-adjusted life year (DALY)-averted studies address this topic. [https://cevr.tuftsmedicalcenter.org/news/2019/combating-cancer-with-cost-effective-strategies](https://cevr.tuftsmedicalcenter.org/news/2019/combating-cancer-with-cost-effective-strategies)

8 Reevaluating Pneumococcal Vaccine Guidance: An Analysis (ScienceDaily)
A University of Pittsburgh School of Medicine analysis says to mitigate race disparities among those who contract pneumococcal diseases such as pneumonia and meningitis, an effective guidance could be to recommend that all adults get a pneumococcal vaccine at age 50. But unless lowering the age for universal vaccination produces double-digit increases in vaccination rates or the vaccine protects against more types of pneumonia than it has been proven to, researchers conclude that it isn’t going to be cost-effective to change the current recommendation. [https://www.sciencedaily.com/releases/2019/03/190304100002.htm](https://www.sciencedaily.com/releases/2019/03/190304100002.htm)

9 Vertex CEO Hints at “New Ideas” to Bring Orkambi to UK Patients (pharmaphorum)
The cystic fibrosis (CF) drug, Orkambi (lumacaftor/ivacaftor), may become available to all patients throughout the United Kingdom as Vertex CEO Jeffrey Leiden is offering several ideas to UK negotiators to break the more than three-year deadlock over the drug’s pricing. Orkambi has been available in Scotland, but not in England. Leiden said he could not accept the NHS’ offer for Orkambi and other CF drugs because it would affect the revenues the company needs to continue with its research into CF and other rare diseases. [https://pharmaphorum.com/news/vertex-ceo-hints-at-new-ideas-to-bring-orkambi-to-uk-patients/](https://pharmaphorum.com/news/vertex-ceo-hints-at-new-ideas-to-bring-orkambi-to-uk-patients/)

10 KFF Health Tracking Poll - February 2019: Prescription Drugs (Kaiser Family Foundation)
In its recent poll, Kaiser Family Foundation has found that while many of those surveyed (80%) blame the pharmaceutical industry for high drug prices, 63% also blame pharmaceutical benefit managers. And while 59% say the drugs developed in the last 20 years have generally improved the lives of people in the United States, 79% say the cost of drugs is “unreasonable.” [https://www.kff.org/health-reform/poll-finding/kff-health-tracking-poll-february-2019-prescription-drugs/](https://www.kff.org/health-reform/poll-finding/kff-health-tracking-poll-february-2019-prescription-drugs/)

11 Value of Medicines 2019 Special Feature: The Unanswered Question of Value (PharmaLive)
With Congressional hearings on drug prices, proposed rules for Medicare plans, and new ICER efforts to link outcomes to value, finding answers on how to price and pay for drugs is still difficult. [https://www.pharmalive.com/value-of-medicines-special-feature-the-unanswered-question-of-value/](https://www.pharmalive.com/value-of-medicines-special-feature-the-unanswered-question-of-value/)

12 The Administration’s Drug Rebate Proposal: An Opportunity to Put Patients First (Morning Consult)
A. Mark Fendrick and Dan Klein express support of the Trump administration’s drug rebate proposal, but add “like most things in health care, there is more complexity to the administration’s proposed changes to pharmaceutical company rebates than initially meets the eye.” [https://morningconsult.com/opinions/administrations-drug-rebate-proposal-opportunity-put-patients-first/](https://morningconsult.com/opinions/administrations-drug-rebate-proposal-opportunity-put-patients-first/)
Next month!

ISPOR 2019

Rapid. Disruptive. Innovative: A New Era in HEOR

May 18-22, 2019
New Orleans Ernest N. Morial Convention Center
New Orleans, LA, USA

Join colleagues to discuss the latest trends in health economics and outcomes research (HEOR) and help shape the future of HEOR. ISPOR is the leading scientific and educational organization for HEOR and its use in healthcare decision making.

Why Attend ISPOR 2019?

ISPOR 2019 will provide a forum for discussion and dissemination of HEOR information for more than 4000 delegates. The conference is a great opportunity to present your work, collaborate and network with colleagues in the field, and hear about innovative research methods and new health policy developments. Reflecting on revolutionary transformations affecting today's healthcare, ISPOR New Orleans will address medical technology development, health technology assessment, and policy and clinical decision making while exploring the theme Rapid. Disruptive. Innovative: A New Era in HEOR.

FIRST PLENARY SESSION: MONDAY, MAY 20, 8:30AM - 10:30AM
The Dawn of Disruption in the Health Sector: Will Innovative Technologies Require Innovative Ways of Thinking?

The healthcare sector has recently witnessed several landmark moments in the development of the next generation of medical care. While media attention has rightly focused on milestone regulatory approvals for several groundbreaking curative treatments and devices, the best is likely yet to come: over 2600 clinical trials of gene therapies are either completed or ongoing; nearly 1000 trials of regenerative medicine are in progress worldwide; and more than 7000 trials for medical devices ranging from bionic eye brain implants to spinal cord stimulators are underway.

Disruption will not be limited to drugs and devices, however. Advances in the applications of 3-D printing as well as artificial intelligence have the potential to generate powerful new tools for disease prevention, diagnosis, and treatment. In short, innovations that have long been the stuff of science fiction may no longer be distant points on the horizon. Are we entering a "golden age" of disruptive innovation in medical care? What new challenges and opportunities will these technologies bring? How can a health sector attuned to an old way of doing things truly prepare for treatments that break the mold? This plenary session will begin with an overview of the current and future landscape followed by a discussion among leading experts. Emerging challenges and opportunities presented by disruptive technologies will be addressed from the perspective of a variety of stakeholders such as payers, manufacturers, and patients.
SECOND PLENARY SESSION: TUESDAY, MAY 21, 8:30AM - 10:30AM
Medical Device Innovation and Regulation: Turbocharged for Success?

The medical implants market is one of the fastest-growing in healthcare. Yet alongside this rapid growth, the industry is facing increasing calls for regulation and oversight. As the demand for innovative medical devices accelerates, how can regulators ensure the highest level of health protection without hindering research and growth in the sector? This tension emerges from the two forces shaping the medical devices market: companies who are driving innovation, eager to bring needed new advances to patients and clinicians as quickly as possible and the regulators, responsible for governing the parameters of these advances.

So how will the latest legislation fare? The new EU Medical Devices Regulation ((EU) 2017/745) will come into force on May 26, 2020 and is intended to "ensure a high level of safety and health while supporting innovation." Other regulators such as the FDA are also instituting major changes to their medical device regulations. How will these new regulations better guarantee patients’ safety and strengthen confidence on the uptake and diffusion of medical devices?

This plenary will explore how our healthcare systems navigate these controversies and identify implications and opportunities for the HEOR community, including the generation of relevant real-world evidence to support better decision-making as well as what further regulations are needed. Finally, the panel will consider how such systems can evolve to keep up with the rapidly-innovating world of medical devices.

THIRD PLENARY SESSION: WEDNESDAY, MAY 22, 11:00AM - 12:30PM
Is Affordability Driving a Need to Revolutionize Drug Pricing?

Promoting rapid and equitable access to promising therapies in an affordable manner is a laudable goal for all health systems. However, with the explosion of high cost, disruptive, and innovative drugs — many of which are promising a cure — payers are facing a crisis of affordability. We are in an era with six-figure cancer treatments, curative and costly gene therapies, ultra-high cost drugs for treating orphan diseases, and even expensive drugs for more common diseases. It is an exciting and promising time for patients, clinicians, and pharmaceutical companies, and a challenging time for payers who must now look beyond cost-effectiveness to address affordability.

The ISPOR 2019 Top 10 HEOR Trends report identified drug spending and pricing as the top trend. In the United States, President Trump launched his Blueprint to Lower Drug Prices in May 2018, and a recent paper from the University of Chicago reported that average total drug spending per hospital admission increased 18.5% between 2015 and 2017. Affordability of pharmaceuticals has become a truly global issue. Is it time for a revolution in how we price, fund, and manage drugs? Are there innovative approaches that can promote access, manage affordability, and still foster innovation? What can be done to significantly improve the transparency of drug prices? How do we ensure equitable access to low- and middle-income countries and disadvantaged populations?

34 pre-conference short courses!

Offered in conjunction with ISPOR 2019 these are a series of 4- and 8-hour training courses, designed to enhance your knowledge and technique in 7 key topic areas (“Tracks”) related to health economics and outcomes research (HEOR). Short courses range in skill level from Introductory to Experienced. The short course offerings at ISPOR 2019 include 4 new courses that explore hot topics relating to value assessment, healthcare systems, health state utility, and real-world data analysis.
ISPOR Latin America 2019

Data and Value in Healthcare: 2020 and Beyond

12-14 September 2019
Bogotá, Colombia

ISPOR Latin America 2019 will center on the theme, “Data and Value in Healthcare: 2020 and Beyond.” The conference will draw more than 1000 regional and international thought leaders and stakeholders in HEOR to share innovative research methods and health policy developments using outcomes research, patient preferences, real-world data, and clinical, economic, and patient-reported outcomes.

The Conference features invited HEOR expert speakers and 2 thought-provoking plenary sessions focusing on timely and important issues facing healthcare systems across Latin America.

FIRST PLENARY SESSION
The Role of Data Supporting an Effective Decision-Making Process

Many of the processes of everyday life have become increasingly automated. The sheer volume and diversity of data that are currently applied to healthcare have grown exponentially as medical technology and integrated solutions have made this information increasingly accessible and useful for healthcare decision makers.

Real-world data extends the usefulness of randomized controlled trials by its ability to include timely data, large sample sizes that enable analysis of subpopulations and less common effects, and real-world practice and behaviors in applied research studies. Research that uses real-world data and real-world evidence are becoming increasingly important to decision makers, and through careful analysis and interpretation, this type of evidence will play an increasing role in informing healthcare decisions.

In this session entitled “The Role of Data Supporting Effective Decision-Making Processes,” different stakeholders will explore how the management of these “data” impact real-life healthcare decisions and resource allocation in Latin America.

SECOND PLENARY SESSION
Value Measurement in 2020: Moving Forward in Low- to Middle-Income Countries

Based on the delivery model of value-based healthcare, “value” is determined by measuring health outcomes against the cost of delivering the outcomes. However, value measurement in health involves some important decisions about what to measure and how. Which key outcomes determine how the efficiency of a health system should be measured? How can the perspectives of all stakeholders be incorporated, thus making patients and providers partners in healthcare decisions? And, how can patients’ access to innovation be effectively managed so that it adds value and improves health system efficiency?

In the session entitled “Value Measurement in 2020: Moving Forward in Low- to Middle-Income Countries,” panelists will present different approaches to increase efficiency in health systems and improve access to patients.

ANTICIPATED: 1000 attendees • 500 presentations • 10 exhibitors • 15 supporting institutions
NEW FOR THIS CONFERENCE: 3 new HEOR short courses
AVAILABLE NOW: conference and short course registration • sponsorship opportunities
REGISTER EARLY AND SAVE: 30 July 2019

JOIN THE CONVERSATION #ISPORLA
Join Us this Fall!

**ISPOR Scientific Summit**

**October 11, 2019**  
**Baltimore, MD, USA**

Join ISPOR and prominent thought leaders in health economics and outcomes research (HEOR) and health policy for ISPOR Summit 2019. ISPOR Summits convene a variety of healthcare stakeholders and provide a forum for discussion, exploration, and debate of critical issues in HEOR and health policy.

**JOIN THE CONVERSATION**  
#ISPORSummit

---

**ISPOR Europe 2019**

**2-6 November 2019**  
**Copenhagen, Denmark**

**ANTICIPATED:**  
5000 attendees • 2400 presentations • 100 exhibitors

**AVAILABLE NOW:**  
call for abstracts • exhibitor and sponsor opportunities

*Help shape the content of this conference by submitting your research abstract, issue panel proposal or workshop proposal to present at ISPOR Europe 2019!*

**ABSTRACT SUBMISSION DEADLINE:**  
12 June 2019

**REGISTRATION INFORMATION:**  
Registration will open in May

**JOIN THE CONVERSATION**  
#ISPOREurope
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 March 2019

HEALTH POLICY ANALYSIS
Challenges with Forecasting Budget Impact: A Case Study of Six ICER Reports
Julia Thornton Snider, Jesse Sussell, Mahlet Gizaw Tebeka, Alicia Gonzalez, Joshua T. Cohen, Peter Neumann

In determining coverage policies, budget impact models (BIM) continue to be an important decision-making tool for many payers despite the inherent challenges in predicting future costs. This article highlights the issue within the context of U.S. formulary decision-making. Retrospective analysis of pharmaceutical sales data was used to estimate actual patient utilization to compare against budget impact results as modelled and reported by an independent body, the Institute for Clinical and Economic Review (ICER) prior to formulary decision. Based on inclusion criteria for types of medical technologies of interest that had been the focus of an ICER review, six ICER studies conducted prior to 2016 were selected for this analysis. Three BIM outputs were collected (aggregate therapy cost, therapy uptake and price) and compared against real-world estimates generated using drug sales data. Two categories of BIM estimates were considered, “predictive” and “contemporaneous”. The first category covered newly approved drugs, and used forecasted future uptake. Note that prior to 2016, according to ICER guidelines, the uptake was assumed to be “unmanaged” – ie without “restraint on utilization” by insurers. The second category investigated treatments already on the market and measured their current managed uptake and budget impact. Representing the former and latter categories, four and two ICER reports were included, respectively.

In order to generate corresponding real-world estimates for results provided in the selected ICER reports, sales data from the IQVIA National Sales Perspective and National Prescription Audit were used. The primary outcome was the annual aggregate treatment cost for the drug included in the ICER BIM analysis. In the study, the aggregate treatment cost was the product of the estimated therapy cost for a single patient, and total uptake for one year. Real-world estimates were constructed to be consistent with the definitions of those used in the ICER report. In terms of year of analysis, most ICER reports did not state the year modelled. In those situations, the authors calculated estimates for the first calendar year following the report.

The analyses found that there were large differences in the real-world data based retrospective estimates compared to the earlier modelled predictions especially for the “predictive” modelled studies, where an “unmanaged uptake” assumption was used. In these, the predicted uptake exceeded ex post real-world estimates by an average of 25-fold. In addition, the modelled aggregated treatment cost exceeded the real-world data, by an average of 36-fold. Prices in the models exceeded those in the real world data estimates by 15%. In the category of “contemporaneous” studies, the modelled uptake estimates were less divergent, but still exceeded real-world estimates by 7.6-fold, while aggregate treatment cost exceeded by 8.6-fold. Interestingly, price estimates were 24% lower than reflected by real-world data.

The authors attribute the overestimation by the models especially within the predictive studies to the ICER’s assumption of “unmanaged uptake” which, since 2016, is no longer used by the ICER organization in its studies. Beyond this, the authors acknowledge that it is impossible to ascertain how much of the differences are due to methodological differences or other factors. In the 2 contemporaneous studies, results were expectedly closer to the authors’ real-world estimates but still larger by several fold. The authors discuss several reasons for this including the possibility of the ICER report itself influencing policy-making and in turn use and access which they term the “ICER effect”.

Although the generalizability from six studies is difficult, this study is of interest as it examines the process of assessment itself. Introspection of the process is equally important in order that the system of assessment and methods used can be improved. Although the study was conducted within a U.S. payer setting, the results provide important lessons to researchers and decision-makers globally. Given the constraints on the health care budget, budget impact modelling continues to be key in decision-making in many settings. High budget impact is often a reason for population restrictions on the use of a health technology. Yet the results and applicability of the model results have rarely been examined after the primary decision. To this reader, although the study does not provide an easy solution to the challenges faced in budget impact modelling particularly in assigning assumptions for novel therapies, it highlights that decision-makers should be aware of and understand the assumptions used within the models as they make critical decisions which determine patient access. It also underlines the value of process reviews and reassessment of technologies, continued transparency in assessment methodology, data source use and decision-making. These can generate understanding and help spur improvements in formulary decision-making.
CALL FOR PAPERS

Systematic Literature Reviews Related to Healthcare Treatments and Policies

Systematic literature reviews are an essential component for obtaining data inputs or assessing the impact of health technologies on clinical, economic, or health-related quality of life. Systematic reviews may inform coverage decisions for drugs, devices, or public health interventions, and frequently are used in comprehensive health technology assessments. When conducted properly, systematic literature reviews pool all relevant data to allow a more efficient process for assessing value. Therefore, a full understanding of systematic reviews—and how to implement them in practice—is imperative for anyone involved in healthcare research, practice, and policy.

Recognizing the inherent usefulness of these types of studies, the Editors of Value in Health are issuing an open Call for Papers for systematic literature reviews on a wide array of topics that seek to inform healthcare decision making. Submissions do not need to focus solely on reviews of randomized controlled trials; they can include reviews of observational studies, economic evaluations, outcomes research studies, and preference-based assessments. Reviews can address any aspect of value in health (e.g., quality of life, resource use, and cost-effectiveness), but papers reporting reviews of studies containing only clinical endpoints are out of scope for this call.

Topics of interest include, but are not limited to:

- Systematic reviews of the value of drugs, devices, procedures, and other health technologies
- Evaluations that provide credible evidence of heterogeneity of treatment effects across comparator health interventions
- Systematic reviews of healthcare policies or the use of methods to assist policy making (e.g., MCDA)
- Methodological articles that address bias or other techniques to produce comprehensive assessments

Submissions received before November 15, 2019 will have the best chance of being published in Value in Health in 2020. Final decisions regarding ultimate acceptance rest solely with the Editors.

Authors should submit manuscripts through the journal’s online submission system at https://mc.manuscriptcentral.com/valueinhealth and be sure to classify their submissions as Systematic Literature Reviews.

www.ispor.org

505 Lawrence Square Blvd South, Lawrenceville, NJ 08648
© 2019 ISPOR – The professional society for health economics and outcomes research
Artificial Intelligence: The Key to Unlocking Novel Real-World Data?

While Artificial intelligence stands to make significant contributions to clinical research due to its unparalleled ability to translate unstructured data into real-world evidence (RWE), significant challenges remain in achieving regulatory-grade evidence.

By Michele Cleary
Artificial intelligence (AI) is revolutionizing healthcare services. From improving disease detection to supporting treatment decision making, AI has become ubiquitous in care delivery.

Now AI is poised to transform the drug and device development process, helping researchers refine the approval process and significantly cutting both the time and the expense needed to bring products to market. While AI has long been used to facilitate recruitment of study subjects, optimize study design, and support patient adherence to study protocols, AI’s greatest contribution to clinical research may still be on the horizon—unlocking the data richness that lies within the mountains of novel real-world data (RWD) sources.

This article explores how AI may improve clinical research through its ability to better translate RWD into real-world evidence (RWE), thus providing more valid evidence of clinical benefits and risks. Dan Riskin, MD, of Verantos, Rich Glinklich, MD of OM1, and Sebastian Schneeweiss, MD of Aetion all shared their valuable insights into how AI is transforming clinical research.

THE SEARCH FOR REGULATORY-GRADE DATA

With innovations in digital data, HEOR researchers are facing explosive growth in novel RWD sources. But as researchers move from traditional RWD sources (eg, registries and claims data) to these novel data sources, unstructured data present a significant opportunity and challenge. These novel data sources include doctor notes, discharge summaries, lab or imaging reports, and even social media posts. Some estimate up to 80% of electronic health record (EHR) data may be unstructured.1,2

The challenge lies in structuring RWD so valid clinical assertions can be made. AI may provide the key to unlocking these unstructured data, helping researchers identify clinically relevant data points critical to the approval process, which currently are not available in structured data fields. In addition to helping trial operations (eg, recruitment), AI can also help researchers process large volumes of disparate novel RWD to identify critical signals of clinical outcomes, including potentially new biomarkers or postmarketing safety signals.

Regulatory parties appear open to AI’s growing role in the development process. The European Medicines Agency (EMA) recently presented its strategic goals regarding how AI may support regulatory decision making, proposing the need to develop AI capabilities to drive “collaborative evidence generation—improving the scientific quality of evaluations.”3 The US Food and Drug Administration (FDA) is also embracing the use of AI to expand the use of novel RWD, with former FDA Commissioner Scott Gottlieb recently stating, “Advancing real-world data into regulatory-quality real-world evidence is a key strategic priority for the FDA.”
In addition to the FDA, other US agencies are welcoming AI. For instance, the Centers for Medicare and Medicaid Services (CMS) recently launched the CMS Artificial Intelligence Health Outcomes Challenge to support private AI innovation to improve the agency’s predictive modeling practices. And the Center for Drug Evaluation and Research’s Office of Surveillance and Epidemiology (OSE) has been exploring ways that AI may improve the agency’s ability to identify and prioritize drug-related adverse event reports.

THE CHALLENGE OF DATA VALIDITY
Perhaps the greatest challenge in using RWD is in making valid clinical assertions. As these data sources are used more frequently not only to assess comparative effectiveness but also to make access determinations, data validity—data accuracy—becomes critically important. According to Dr Riskin, “If we’re changing the standard of care based on clinical assertions, then data validity matters. And in our world, data validity breaks down to data accuracy and data generalizability.”

Clinical assertions made from administrative claims data have long been known to carry uncertain validity. Billing codes do not necessarily represent clinical conditions, especially when upcoding occurs. Nor do they differentiate between ruling out a diagnosis or confirming a diagnosis. But per Dr Glinklkh, “Some data are better than no data with respect to safety signal.”

To improve data validity, data abstractors have been used to evaluate the unstructured data within other RWD sources, such as EHRs or imaging reports. When budgets allowed, multiple abstractors could be deployed to improve accuracy. But data accuracy is still limited by differences across abstractors. And given the time and budget demands, abstraction is rarely an efficient approach to achieving data validity.

MAKING RWD USABLE THROUGH AI
AI can improve the validity of clinical assessments derived from novel RWD through natural language processing (NLP) and machine learning (ML).

NLP is a common first step to AI. NLP involves linking words, phrases, and terms listed within unstructured data (physician notes) to indicate a specific condition or event. For instance, physicians may use a mix of terms to indicate the patient has had a recent myocardial infarction (MI): “heart attack,” “MI,” “myocardial infarct.” NLP must differentiate between “rule out MI” and confirm MI. Common NLP techniques used to abstract these clinical indicators include simple word-based models for text classification, structured models for syntactic parsing (recognizing a sentence and assigning a syntactic structure to it), collocation finding (finding sequence of words or terms which co-occur more often than would be expected by chance), word-sense disambiguation (identifying which sense of a word is used in a sentence), and machine translation (translation of text by computer with no human involvement). However, while an improvement over billing codes, NLP provides only marginal improvement in data accuracy over abstraction.

Between NLP and ML lies inference, whereby computer programs search for patterns across data sources to infer a condition. For instance, searching a patient’s EHR, the program may find troponin, EKG changes, chest pain—signs of a probable MI.

THE IMPORTANCE OF DESIGN
While many life science companies are currently using NLP techniques in their drug approval research, and some have introduced inference methods, these AI-aided results may still be insufficient to show an effect size.

Dr Riskin proposes going further by incorporating ML, arguing that NLP could achieve data accuracy levels of approximately 85%. If the effect size in the study is a 10% to 20% difference in groups, that level of data accuracy will be insufficient. ML including pattern recognition increases accuracy levels above 90%, sufficient to make valid clinical assertions.

ML offers the most sophisticated analysis, utilizing algorithms and statistical models to simulate human learning. ML algorithms may include patient demographic data, such as age, gender, and disease history, as well as relevant disease-specific data, such as diagnostic imaging, gene expressions, physical examination results, clinical symptoms, or medications. ML has been used extensively in oncology and immunology, translating imaging and digital pathology into usable clinical data that help clarify treatment choices and transform oncology care. The use of ML in these disease areas is not unexpected given their reliance on imaging and genetic data—deciphering these types of data is an AI strength.

Dr Schneeweiss identified 2 key ML use cases. The first is causal inference, for which ML would help identify additional covariates and new causal inference techniques, such as collaborative targeted maximum-likelihood estimates. The second use case is for predictive analytics, where ML could help target those patients who may best respond to a given treatment.

One key advantage of ML is its ability to operate on numerous predictive features in datasets including outliers, noise, and collinearities, without the stability and reliability concerns of traditional statistical modeling. This enables complex patterns and interactions to be identified. Using pattern similarities between patients with or without a given diagnosis, this approach can confirm a diagnosis in patients for whom the disease is present but is undiagnosed or underdiagnosed. As the volume of RWD continues to grow, so will the demand for sound ML. For as Dr Schneeweiss emphasized, “The less structured the information is, the more helpful machine learning will be.”
WHAT IS NEEDED FOR GOOD AI?

To fully employ the benefits of AI, computing prowess alone is not sufficient.

Dr Riskin argued that good AI requires the right technologies, good scientific design, and the right data sources.

By the right technologies, he called for using all 3 AI approaches discussed here—NLP, inference, and ML. Next, he emphasized that good scientific design, namely knowing the expected effect size in advance through proper study design, is critical. This step identifies what the level of required accuracy will be in advance of running the study and then checking accuracy during the study. While rigorous chart abstraction and NLP may improve specificity, it may not improve sensitivity, so both aspects of accuracy need to be protocollled and tested. Finally, he strongly encouraged the use of more-advanced data sets with rich, unstructured data linked at the patient level to extend research capabilities beyond those allowed with traditional RWE (eg, registries) or randomized controlled trials (RCTs).

ACCEPTANCE OF AI DATA

Currently, the FDA is evaluating which models may be appropriate for regulatory safety or approval decision making. Dr Glinklich emphasized that acceptance of AI data will be dependent upon how comfortable end users of AI data are with performance characteristics. He noted that positive predictive value in detecting safety events within unstructured data must pass a certain threshold in order to gain acceptance by regulatory bodies. He stated that “as we move into other areas of how AI might be used with unstructured data to generate a usable signal of safety, effectiveness, or efficacy, will depend on generalized performance metrics that are understood, validated, standardized, and surpass known thresholds.”

THE DISCUSSION CONTINUES

ISPOR continues its discussion on AI application within the drug and device development process during its 2019 Conference in New Orleans, Louisiana. ISPOR will be hosting “Global Developments in Artificial Intelligence and Machine Learning in Healthcare.” This Spotlight Session will focus on trends in AI and ML from the perspectives of North America, Europe, and the Asia Pacific regions. Presenters will address issues surrounding causal inference, as well as the differences between unsupervised and supervised methods within ML. Presenters will also review how AI and ML methods are currently being used in healthcare delivery, drug discovery, health technology assessment, regulatory approval, and safety surveillance. The session will close with presenters forecasting how AI use may evolve over the next decade.

Recently the European Commission acted to increase the availability of healthcare data sharing through the Digital Single Market. European Commissioner for the Digital Single Market and Vice-President Andrus Ansip said, “The Digital Single Market is rapidly taking shape; but without data, we will not make the most of artificial intelligence, high-performance computing, and other technological advances. These technologies can help us to improve healthcare.”

As RWD sources continue to expand, so will the need for sound AI methods. ISPOR looks forward to engaging researchers, regulatory bodies, and other stakeholders during the 2019 ISPOR Conference to advance AI applications in clinical research.

REFERENCES


ABOUT THE AUTHOR

Michele Cleary is an HEOR researcher and scientific writer with more than 15 years of experience in the healthcare field.


**By the Numbers: Artificial Intelligence in Health - Trial and Tribulations**

Section Editor: The ISPOR Student Network

---

**TIMELINE ON ARTIFICIAL INTELLIGENCE IN MEDICINE**

1920
Karel Capek, a Czech novelist and playwright, coins the term “robot”

1950
Invention of the Turing test to determine a machine’s ability to exhibit intelligent behavior

1955
John McCarthy introduces the term “artificial intelligence”

1997
IBM’s Deep Blue computer defeats chess champion Garry Kasparov

2011
IBM’s Watson computer wins Jeopardy, playing against top champions

2013
MD Anderson Cancer Center and IBM announce plans to develop the IBM Watson-powered Oncology Expert Advisor1

2014
Amazon introduces its virtual assistant Alexa, which WebMD and health systems now use to retrieve general health information

2015
Google-owned DeepMind Health partners with the U.K.’s National Health Service (NHS) to access their health records2

2017
MD Anderson Cancer Center puts its IBM Watson project on hold3

2018
US-FDA approves first artificial intelligence device to detect diabetic retinopathy4

2019
US-FDA announces “Digital Health Innovation Action Plan” to streamline timely approval of artificial intelligence products5

References:

---

**Number of Artificial Intelligence companies by Country in 2017**

![Number of Artificial Intelligence companies by Country in 2017](image)

---

**Healthcare Consumers’ Opinion on why (not) to use an Artificial Intelligence-powered Virtual Doctor**

**REASONS FOR PREFERING A VIRTUAL VS. A REAL DOCTOR**

<table>
<thead>
<tr>
<th>VIRTUAL DOCTOR</th>
<th>REAL DOCTOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>47% Available whenever needed</td>
<td>29% Liking to visit the doctor</td>
</tr>
<tr>
<td>36% Saves traveling time</td>
<td>26% Lack of knowledge on AI</td>
</tr>
<tr>
<td>24% Assesses vast amounts of info</td>
<td>23% Don’t want to share data</td>
</tr>
</tbody>
</table>

**ADVANTAGES OF A VIRTUAL VS. A REAL DOCTOR**

<table>
<thead>
<tr>
<th>VIRTUAL DOCTOR</th>
<th>REAL DOCTOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>54% Reducing costs to patients</td>
<td>64% Providing quality care</td>
</tr>
<tr>
<td>49% Accommodating patients’ schedules</td>
<td>60% Patient engagement</td>
</tr>
<tr>
<td>43% Providing timely care</td>
<td>45% Diagnosing problems faster</td>
</tr>
</tbody>
</table>

References:

Contributors:
Judith John, Kerala University of Health Sciences, India; Christy Choi, University of Minnesota, USA; Shannon Vaffis, University of Arizona, USA; Aakash Gandhi, University of Maryland, USA; Laura Gressler, University of Maryland, USA; George Okoli, University of Manitoba, Canada; Nazneen Shaikh, West Virginia University, USA; Jayesh Patel, West Virginia University, USA; Koen Degeling, University of Twente, Netherlands
HEOR is changing at a rapid pace.
Let ISPOR guide you through it.

Join a global network of more than 20,000 healthcare professionals who are improving healthcare decisions

Members enjoy:
- Admission to a global network of diverse healthcare stakeholders
- Access to healthcare’s key influencers, from payers and providers to researchers and patients
- Discounts on event registrations
- Subscriptions to all ISPOR publications
- Special awards and recognition
- Exclusive online HEOR tools and cutting-edge science
- Knowledge-sharing opportunities with ISPOR colleagues

New to the field? Explore ISPOR member perks like private career development resources, members-only education and training programs, and exclusive networking opportunities!

Take advantage of your ISPOR membership
www.ispor.org/GetInvolved

www.ispor.org
Is Artificial Intelligence the Next Big Thing in Health Economics and Outcomes Research?

Juan-David Rueda, MD, MS, University of Maryland School of Pharmacy, Baltimore, MD, USA; Rafael Alfonso Cristancho, MD, MS, PhD, GlaxoSmithKline, Collegeville, PA, USA; and Julia F. Slejko, PhD, University of Maryland School of Pharmacy, Baltimore, MD, USA

To harness the enormous potential of AI in health economics and outcomes research, we need to improve the quality of healthcare information systems and data, train researchers and decision makers on these methods and applications, and define some basic guidelines for any AI-driven research activity.

The human brain has several capabilities that make it unique, including perception, learning, problem solving, decision making, linguistic abstraction and generalization, creativity, pattern recognition, forecasting and more. Intelligence is the ability to understand an issue or problem, and by applying previous knowledge, solve it. Artificial intelligence (AI) is the use of machines to perform processes that mimic this capability.1 AI integrates multiple cognitive functions to sense, cognize, and perform tasks.

While AI can be classified in multiple ways, the most-used definition divides AI into 2 broad categories: strong AI and weak AI. Strong AI refers to the concept that machines can think and perform tasks on their own, just like a human being, with little to no human interaction. This has been depicted in popular films and television. Weak AI is much more focused and frequently used. Its goal is to solve a specific task, e.g., finding the best route on your smartphone or using an application that recommends music or films based on your preferences, like Pandora™ or Netflix™. Nonetheless, other subcategories of AI offer vast potential to explore, such as image recognition, natural language processing, expert systems, speech, planning, and robotics, among many others.1

AI research and its applications in data analysis have been adopted rapidly in other fields, particularly in technology and marketing. In healthcare, with the increasing use of information systems, the access to large amounts of data across the healthcare systems and potentially, from other sources that routinely collect health-related data, leverage these applications and optimize many processes and decisions. Specifically, in the field of health economics and outcomes research (HEOR), we rely on healthcare systems data, such as administrative claims or electronic health records, to leverage these applications and optimize many processes and decisions. Specifically, in the field of health economics and outcomes research (HEOR), we rely on healthcare systems data, such as administrative claims or electronic health records, to generate evidence that can help to inform decision for patients, providers, healthcare systems, and policy makers.

We have identified potential opportunities for using AI in HEOR, matching 4 well-established applications of AI: 1) natural language processing; 2) text data analysis; 3) machine learning (ML); and 4) deep learning (Figure 1), to 5 of the most common types of HEOR research activities: 1) burden of illness; 2) drug utilization and patterns of use; 3) patient-reported outcomes (PRO); 4) comparative-effectiveness research (CER); and 5) economic evaluations (Table 1).

NATURAL LANGUAGE PROCESSING
Natural language processing (NLP) is the field that aims to make human language easier for machines to understand. In this context, AI technology can help in the automation of data extraction from unstructured documents like medical records and electronic health records, which can be used to support the generation of evidence in HEOR studies.

Table 1. Potential for Use of AI in HEOR by Study Type

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Natural Language Processing</th>
<th>Text Data Analysis</th>
<th>Machine Learning</th>
<th>Deep Learning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burden of Illness</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Drug Utilization and Patterns of Use</td>
<td>+++</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Patient-Reported Outcomes</td>
<td>+++</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Comparative Effectiveness Research</td>
<td>++</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Economic Evaluations</td>
<td>++</td>
<td></td>
<td></td>
<td>+++</td>
</tr>
</tbody>
</table>

The rating represents the strength of the application of each method to the HEOR research activities. + = less applicability; +++ = high applicability.
all the time: Siri, Alexa, Google Home, etc. The objective of NLP is not only to establish the structure between words in a text (syntax) but also to understand the meaning (semantics) and the context meaning (pragmatics). Algorithms that use NLP have been implemented in chatbots, making them capable of applying deductive coding (supervised ML) and inductive coding (unsupervised ML). In this context, the chatbot is trying to identify common themes from the source file or document, similar to the job performed by a human researcher when coding qualitative data.

In the first approach, supervised ML, a “code book” is used to link each one of the sentences in the interview. The second, unsupervised ML is more exploratory, allowing the chatbot to compile sentences that seem related to a given theme. This application could be used easily in PRO research. There is also an interesting potential application of this technology to the identification of adverse events, or other outcomes not routinely or consistently coded in electronic medical records (EMRs) and frequently used in drug utilization, CER, and PRO studies. Performing systematic scanning of open fields with text in EMRs or physician dictation notes, NLP could capture and analyze additional information to confirm and contrast the findings using only structured data fields or codes.

**TEXT DATA ANALYSIS/TEXT MINING**

Text data analysis or text mining refers to the conversion of unstructured text data into structured data. The concepts of text data analysis overlap with NLP and data mining, but text mining is limited to written sources. Text mining identifies syntax, semantics, and pragmatics that would otherwise remain hidden in a written document. Rather than a simple keyword search, the machine uses text data analysis to read and analyze documents. EMRs and medical and prescription claims datasets commonly have structured and unstructured data that contain valuable medical information and are used frequently in research. However, discrepancies exist between codes used for billing purposes and the notes from the doctor’s office. Combing through medical records’ unstructured data is time-consuming and difficult to standardize. Text data analysis can make this process much more efficient to enhance the implementation of CER and to generate real-world evidence. Already some companies are using these technologies to facilitate the development of systematic reviews, for example IBM Watson™ and Doctor Evidence™.

**MACHINE—OR STATISTICAL—LEARNING**

Machine—or statistical—learning has a great potential for application in HEOR for its ability to learn and perform tasks. ML, named as such because to acquire new knowledge, the machine “learns” from experience and tunes the algorithms over time, requires vast amounts of data. Its goal is to transform data into intelligent action and perform a specific task. Models that use clinical and demographic information for prediction of events, such as severe exacerbations in patients with asthma; or to diagnose a condition using specific patterns applied to image recognition, for instance, diagnosis of a genetic syndrome using face photography; or using voice recognition to detect changes related to dementia; are just a few examples of current applications.

One of the most commonly used ML algorithms is neural networks. A neural network mimics the structure of the cells in the human brain. Neurons are connected through synapses. In a neural network, multiple layers of algorithms (neurons) feed data into other algorithms, creating a very intricate system to perform a specific task. This system comprises 3 layers: the input layer, or original data; the hidden layer, or “black box”; and the output layer, which is the specific task performed. Similar to the brain, the explanation of the interaction of neurons is meaningless; the relevance is focused on the outputs obtained that are tangible and improve over time. If we define clear, specific rules linked to a dynamic dataset with the relevant inputs for updating or for the adaptation of a previously developed economic model, the machine could perform this task using neural networks and update the results in real time for multiple countries or healthcare systems, based on the data available.

**DEEP LEARNING**

Deep learning refers to the process of understanding large amounts of data with multiple hidden layers in a neural network, increasing the computing power over very large and complex datasets. Burden of illness studies, which are aimed to determine the healthcare resource use, costs, and humanitarian impact of a given condition, will require data from multiple sources, including patients, providers, and health care systems. Often, a combination of datasets from epidemiologic surveys or registries, claims datasets, and patient surveys are used in order to achieve this goal. The application of deep-learning techniques could perform these analyses more efficiently.

The use and impact of AI on our daily activities are undeniable. AI helps us connect to each other, decide what to watch or listen and what or when to buy, and often, answers our questions faster than ever before. Nonetheless, in healthcare and research, the adoption of AI is just starting, and many barriers and challenges are emerging. For example, the collection and use of private data is increasing across many different platforms but it still unclear how that data can or will be used in the future by those who already have the information or are collecting it. >
Fresh in our minds is the recent Facebook data breach, exposing more than 50 million users.[10]

Privacy issues can be even more sensitive with medical and other health records, which may be subject to similar security risks. Some ethical concerns have been raised as well, specifically regarding the potential of AI to favor some subgroups simply based on having more or better information, similar to the traditional information bias but at a different level. Along the same lines, access to technology and AI applications and its potential benefits is not the same for everyone, potentially increasing certain disparities. Finally, the quality of the data, as with many other data-driven applications, will determine the quality of the results. In our field, data quality is heterogeneous and can lead to hidden errors that are difficult to identify.

In order to harness the enormous potential of AI in HEOR, we need to improve the quality of healthcare information systems and data, train researchers and decision makers on these methods and applications, and define some basic guidelines for any AI-driven research activity.

REFERENCES

The use and impact of AI on our daily activities are undeniable. AI helps us connect to each other, decide what to watch or listen and what or when to buy, and often, answers our questions faster than ever before. Nonetheless, in healthcare and research, the adoption of AI is just starting, and many barriers and challenges are emerging.

As we described above, many processes inside AI can become too complex or difficult to understand, like a black box, that is difficult to report and in some cases could be proprietary, limiting reproducibility. We advocate for full transparency of methods, data, and algorithms. Currently, there is no guidance in the reporting of models that use AI (specifically ML) in our field. Finally, as many have predicted in the movies, we could encounter a critical issue known in AI as the “control problem.” This problem can be summarized as: How can we create machines that help us without harming us? This could be a problem if AI is assigned to maximize goals but finds an undesirable solution, as illustrated by the Greek myth of King Midas or more recently, in the HBO series Westworld.
A Health Economist Walks Into a Tech Company: Principles for Reproducible Real-World Analyses

Blythe Adamson, PhD, MPH, Josh Kraut, MA, Carrie Bennette, PhD, MPH, Flatiron Health, New York, NY, USA

The oncologist struggled to find the right words. The scientific publication upon which she based her most recent treatment recommendation for the patient sitting in front of her had just been retracted from a prestigious journal. She reflected on a lengthy discussion with this patient 6 months prior considering the trade-offs between treatment options. Balancing the evidence of efficacy, value of hope, and impact on quality of life was difficult enough when based on accurate and reliable research. The retracted comparative-effectiveness study that had once embodied so much promise now brought bitterness and confusion.

The cost of bad clinical research often extends beyond these intimate conversations to the broader scientific field. Scientific advances are almost universally incremental; they build upon the foundation laid by the previous generation. If that foundation turns out to be unstable, entire research areas that were built on top of it can crumble.

For centuries, the responsibility to identify mistakes in scientific research has fallen largely on the shoulders of peer reviewers. They are challenged to evaluate the integrity and accuracy of a manuscript critically. Peer reviewers can be “generous” to the authors by giving them the benefit of the doubt and assuming the black box of methods described is full of the rigorous tools we expect. However, unfortunately, manuscripts are often missing detailed methods, analysis code, and/or the raw data necessary to check computationally intensive research critically. As fields like HEOR embrace the enormous potential of “big data” and become increasingly reliant on modern scientific computing tools to answer important research questions, the gap between what is included in a written manuscript and what is needed to evaluate the research critically grows.

HOW DO WE KNOW IF THE RESULTS OF STUDIES ARE ACCURATE?
The first step is simple: reproducibility. But how do you define “reproducible”? Does it simply mean other people in your organization can run your analysis code on their machine? Or if we asked a stranger to read one of your publications and you handed them the raw data, should they find the exact same answer if they tried to recreate the analysis? Years from now, when I want to update an old analysis with new data, will I be able to dust off my old code, understand it, and run the analysis again?

There are 2 main reasons why we need to ensure research is reproducible. First, we must show evidence that methods and results are accurate (improve transparency). This reduces uncertainty for decision makers and peer reviewers. Second, we must enable others to make use of and/or build on the methods and results. This is needed to accelerate the development of new medicines.

Although reproducibility correlates with better science, it is no guarantee. Recent discussions of the book, *Rigor Mortis: How Sloppy Science Creates Worthless Cures, Crushes Hope, and Wastes Billions*, by NPR Scientific Correspondent Richard Harris created waves of realization and plans for reformation in the research community.

Discussions in the media and in scientific literature have recently emphasized the importance of reproducible research, including a special issue of the journal *Science*.

The need to use more-reproducible tools in HEOR is growing rapidly as analyses of real-world data become more frequent, involve larger datasets, and employ more complex computations. Data scientists now demand and support the curation of high-quality data—aligning with regulatory agencies, health technology authorities, clinicians, patients and healthcare payers around the world that demand high-quality, real-world evidence to make decisions.

THINGS SOFTWARE ENGINEERS CAN TEACH US
Transformation of messy data into meaningful evidence often needs teams of researchers from different disciplines working together with clear
WHAT IS “GOOD” CODE?
We follow and teach these guiding principles for reproducible code:
1. Specify your analysis plan prior to accessing your dataset
2. Write with an audience in mind
3. Do not repeat yourself
4. Code should be modular and reusable
5. Code should be version controlled

In today’s digital data era, it can be very easy for scientists to simply test many different analytic approaches to their dataset and cherry-pick the results that are best suited for their research aims. To prevent this type of behavior, it is critical for scientists to define their analytic protocol prior to undertaking the analysis step and stick to the protocol. Today’s software may make it easy for scientists to iterate over their analysis many times, but this opens the door for introducing a type 1 error.

Importantly, we should all strive to write human-readable code. Analysis code should be easy for anyone on your team and your future self to look at and understand what it is doing. Writing readable code reduces errors and increases efficiency during code review and when revisiting old analyses. To that end, analytic code should aim to create a narrative story that is easy for readers to follow. Even if you don’t think someone else will be looking at your code, assume you are going to end up looking at it down the road and that you’ll have no idea what you were thinking when you wrote it.

Writing functions is one of the building blocks to writing reusable and robust analytic code. Well-written functions help make your intent clear. They can reduce copy/paste mistakes and make updating and testing your code easier. Our guiding best practices for writing functions include: 1) keep them short, 2) do one thing and do it well, and 3) use intuitive names.

Finally, the use of formal version control systems like Git and SVN provide critical functionality for tracking changes made to code. In addition to allowing users to formally keep a working record of all changes to a project’s code, version control systems allow for easy collaboration between code authors and provide built-in mechanisms that make it easier for code authors to review another’s code. These version control tools help code authors manage their analysis and ensure that specific versions of an analysis can easily be recalled later.

FREE TOOLS AVAILABLE TO HELP YOU
Excellent tools for publishing and sharing reproducible documents are commonplace in data science organizations at technology companies, although they are rarely utilized in academic research. We use and have had great success with R, Python, Rstudio, and Jupyter for writing scientific code. These are free, open-source, and exponentially growing in use. The utilization of Integrated Development Environments (IDEs) like Rstudio and Jupyter can make it easier for less-technical scientists to interact with computational analyses.

Using open-source programming languages and tools has many benefits. The key benefit of markdown-based notebooks (Rmarkdown, Jupyter) is the ability to keep your analysis code and output all in one place—the concept of literate statistical programming. Copying and pasting results from SAS/STATA output is no longer accepted as reproducible. Modern open-source programming languages also make it easy to communicate results with colleagues. By running a single command, R and Python file scan automatically and reproducibly write and export beautiful html web pages, Microsoft Word documents, and publication-worthy PDFs.

Packages can be built for internal use in an organization to ensure that analysts implement methods consistently between people and over time. Within the R universe, Hadley Wickham, the data scientist who pioneered the concept of “tidy data,” has assembled an entire “tidyverse” of packages to help wrangle messy real-world data into tidy data. Within the Python universe, Wes McKinney’s “pandas” library is widely used for tabular data analysis.

REFERENCES

ADDITIONAL INFORMATION
Truly, Broadly, and Deeply: How Dynamic Visualizations Are Changing the Way We Understand and Communicate HEOR Findings

Shelagh Szabo, MSc, Broadstreet Health Economics and Outcomes Research, Vancouver, BC, Canada; Ross Tsuyuki, BSc(Pharm), PharmD, MSc, University of Alberta, Edmonton, AB, Canada; and Andrew Lloyd, DPhil, AcasterLloyd Consulting, London, UK

Traditional, data presented statically—like numbers in tables—have been the norm in the fields of epidemiology, health outcomes, and pharmaco economics. However, the science of data visualization is changing that. At first glance, displaying data in a manner that is dynamic and interactive might seem like a gimmick, something to “dumb down” and “pretty up” information for less technical audiences, but the reality is far more complex (and important). Visual patterns and displays can convey data, meaning, and effects far more effectively than language, and people can digest complex ideas far more easily in a visual format. Pharmacoeconomics is a data-heavy field, where findings need to be communicated fairly and accurately to audiences of clinicians, the general public, and policy and decision makers. Data visualization methods—which have been used extensively in a number of other fields but have not been widely taken up yet in health economics and outcomes research (HEOR)—can support these communication and decision-making processes.

At the ISPOR’s 2018 annual meeting in Baltimore, the authors presented a workshop on potential applications of data visualization in HEOR. For many of the attendees, visual translation of data has become a client expectation and participants in the workshop were interested in how to deliver on that. But while the participants at the workshop were cognizant of the availability of off-the-shelf software tools for presenting data visually, many had yet to see the technology used to present complex HEOR and epidemiology data in a more dynamic manner.

---

**Figure 1.** John Snow’s cholera map (note, this image is in the public domain)¹¹
VISUALS IN HEALTH INFORMATION COMMUNICATION ARE NOT NEW

Static data visualization has had a surprisingly long and occasionally vital role in the communication of health information, particularly for informing nontechnical audiences. One of the most famous examples is John Snow’s cholera map from London in the 1850s (Figure 1). The map provided a critical understanding of the relationship between the source of infection—a water pump on Broad Street—and the distribution of cholera cases. Black is used to indicate the presence of cholera at an individual address and the length of the mark, the number of cases. Position illustrates the geographic spread of the disease, but also provides insight into where there was a lack of disease. The map helped facilitate public health reforms to stop the spread of infection and the development of infrastructure to avoid future outbreaks, because it was able to simply communicate the evidence on the source of disease to a broad audience.

Florence Nightingale’s Coxcomb charts (Figure 2) are another example where information presented graphically achieved change where words and text had failed by influencing decision makers to effect public health reform. As a nurse tending to the wounded during the Crimean war, Nightingale saw the impact of poor sanitation in hospitals. However, she struggled to make officials understand that deficiencies in hygiene were killing more soldiers than actual battles. Realizing that images would tell a more powerful story than numbers alone, she created the Coxcomb charts to illustrate how avoidable or treatable conditions were responsible for more deaths than battle wounds. In the image, the small red and black segments at the circle’s center indicate deaths due to battle wounds and the large gray areas, deaths due to other causes. The position around the circle represents the month and the size of the segment, the number of deaths. These diagrams enabled Florence Nightingale to illustrate the magnitude of the problem to decision makers and as a result, her campaign for improving hospital conditions was taken more seriously.

Snow and Nightingale used their static data visualizations successfully to provide critical evidence that led to government healthcare reform. What is common to both visualizations is that they clearly and effectively tell a compelling story, with each element of the image—color, shape, and space—communicating a particular aspect. These tenets of visual storytelling, the economical use of visual elements to synthesize a vast amount of complex information, have been retained as data visualization has evolved. What is new is the added element of interactivity.

INTERACTIVITY ADDS A NEW DIMENSION

Interactivity in visualizations allows for the incorporation of even more layers of data and the communication of more complex concepts. There are excellent examples of the use of interactive visualizations to explore and explain changing demographics and health statistics from a global perspective—the World Health Organization and Gapminder are 2 organizations that provide well-designed online tools for these. However, these types of tools are only now starting to be developed in HEOR. As part of the workshop, examples were presented of the use of interactive data visualizations to display the findings of pharmacoeconomic, patient-reported outcomes, and network meta-analysis studies; these are discussed in more detail below.

The first visualization was of a cost-effectiveness model created on behalf of the Canadian Pharmacists Association demonstrating the benefits of pharmacist prescribing in hypertension care. This model is a modern example of the role for data visualization in advocacy—taking complex data, with results that can have a real public health impact and presenting them in a way that is accessible to a wide range of audiences. Hypertension is a leading cause of premature morbidity and mortality worldwide, and the magnitude of the problem is worsening. The results of several randomized controlled trials have identified that involving community pharmacists in care improves outcomes among patients with hypertension, presumably by lowering barriers for optimal medication titration and monitoring. What has been less clear is the cost-effectiveness of this solution. To evaluate this, a model looking at the impact of various levels of pharmacist intervention in patient care—up to and including the ability to prescribe and make adjustments to prescriptions for medication—on systolic blood pressure among patients with poorly controlled hypertension was developed. The study concluded that pharmacist care facilitates better blood pressure outcomes and results in a savings of $6364 per patient over a lifetime. If applied to just half of the roughly 1.86 million Canadians with uncontrolled hypertension, over 500,000
cardiovascular events would be avoided, for a total cost savings of CDN$15.7B over 30 years.

The robustness of the model results was explored through an interactive “sensitivity analysis” tool (figure 3). The tool allows a skeptical audience to test assumptions of the model, with users able to manipulate and set the level and costs of intervention, the time horizon, and patient populations. The tool is highly customizable, giving the platform the potential to be of international relevance. This is important as HEOR analyses are often used across multiple jurisdictions, targeting a variety of stakeholders, with multiple subgroups and scenarios of interest; customizable interfaces such as this allow for a single analysis to be adapted without the need for voluminous static tables and figures to be generated for all outputs of interest.

The second example is not from the fields of epidemiology or pharmacoeconomics but instead illustrates how HEOR practitioners can learn from what others are doing in data visualization science. The example is an animation published in the New York Times in March 2018 comparing the income mobility from birth to late 30s of African American and white men born into wealthy American families. The animated plot garnered quite a bit of attention on social media because of how directly it communicated the fact that black men (who were born wealthy) were far more likely to fall into poverty than their white contemporaries. So how does this relate to HEOR? Traditionally, we might have used a series of cumulative density-function graphs to display changes in a scale score at different time points. Now think about using the same style of animated graphic that the New York Times did to present results of studies describing changes in outcome measures over time at an individual patient level. It could present the trajectory of all patients in a clinical study for selected outcomes, with color coding to represent different trial arms. Such a visualization could powerfully display the beneficial effect of a treatment over time and the limitations caused by missing data and patient dropouts. A good visualization provides a way of understanding effects
in the study as well as just presenting the data. The dynamism of the image with the movement of the dots clearly communicates change over time, while color and position easily transmit further details such as patient characteristics.

A final example focuses on displaying the inputs and outputs of network meta-analysis (NMA) to characterize comparative safety and efficacy. Interpreting the synthesized output of an NMA requires simultaneous consideration of numerous underlying study and population characteristic. Additionally, multiple analytic approaches are undertaken and for large syntheses involving multiple networks, the amount of output can be onerous to review. Data visualization techniques could have an important exploratory and explanatory role here, too; for example, visually explore the impact of heterogeneity, display uncertainty in estimated effect sizes, and compare output across different analytic parameters. A method for visualizing NMA simply and effectively is presented in Figure 4. A dynamic version of the traditionally static network diagram was created where input features can be specified and manipulated, allowing the user to easily assess the full range of outcomes. Features such as study sample size, number of studies, and strength of effect are incorporated visually using established best practices for data visualization, to maximize the amount of information presented simultaneously. The visualization, programmable by using a variety of software options and customizable to the parameters of any NMA, would ideally allow a non-technical audience to better engage with the underlying data and analytic output.

**THE FUTURE OF HEOR DATA PRESENTATION**

Data visualization has the potential to make the work of communicating the results of all types of HEOR studies more effective and dynamic. If done correctly, a data visualization can be a powerful tool to quickly encapsulate and communicate study findings and encourage varied audiences to interact with the data. It is also shared more easily on social media. But beyond that, the visual medium speaks to the brain in a way that tabular and text data struggle to—information becomes both more accessible and understandable in greater depth. Effectively and accurately visualizing data can help ensure that researchers, clinicians, and decision makers can understand, digest, and communicate the data, all of which are critical for achieving the ultimate goal of improving patient outcomes.

While interactive visualizations have great potential to aid in knowledge dissemination in HEOR, they must be approached carefully to ensure that they are balanced, unbiased reflections of the underlying data. The development of good practice guidelines may be an important next step in helping to steer HEOR researchers during their adoption of this powerful new technology.

**REFERENCES**

Value & Outcomes Spotlight had the opportunity to interview Eric Topol, MD, Founder and Director of the Scripps Research Translational Institute (SRTI), Professor, Molecular Medicine, and Executive Vice-President of Scripps Research. As a researcher, he has published over 1200 peer-reviewed articles, with more than 230,000 citations, elected to the National Academy of Medicine, and is one of the top 10 most cited researchers in medicine (Thomson Reuters ISI, “Doctor of the Decade”). His principal scientific focus has been on the genomic and digital tools to individualize medicine—and the power that brings to individuals to drive the future of medicine.

In 2016, Dr Topol was awarded a $207M grant from the NIH to lead a significant part of the Precision Medicine (All of Us) Initiative, a prospective research program that aims to enroll 1 million participants in the US. Prior to coming to lead Scripps SRTI in 2007, for which he is the principal investigator of a flagship $35M NIH CTSA grant, he led the Cleveland Clinic to become the #1 center for heart care and was the founder of a new medical school there. He has been voted as the #1 most influential physician leader in the United States in a national poll conducted by Modern Healthcare. Besides editing several textbooks, he has published 2 bestseller books on the future of medicine: The Creative Destruction of Medicine and The Patient Will See You Now. His new book, Deep Medicine: How Artificial Intelligence Can Make Health Care Human Again, was just published in 2019.

Value & Outcomes Spotlight: How did you, as a cardiologist by training, come to be interested in such “techie” issues as digital medicine, big data, and artificial intelligence?

Topol: My background in college was in genetics, which was related to an early interest in deep understanding of what makes humans tick. With the convergence of sequencing, biosensors, and enormous data output that was getting momentum in the past decade, I was both enthralled and enamored by its potential to take medicine forward.

Much of your recent work, such as in your book, The Patient Will See You Now, highlights how digital medicine stands to revolutionize patient care. ISPOR has a strong interest in research; what are your thoughts on technological innovations in clinical trials and health outcomes research?

The ability to perform digital clinical trials, without sites, and direct to participant (DIP) is something that has remarkable allure because of its efficiency, low cost, speed, and appeal to both participants and researchers. In the era of mobile devices and hyper-connectivity, this model, as we used in the MS to PS trial published last summer in JAMA, should be used as much as possible. That’s the beauty of using sensors, both wearable for the individual and environmental. Finally we can get to real-world evidence (RWE), which is so much more useful than much of the evidence we’ve relied upon in the history of medicine.

You also have a strong interest in personalized medicine, how do you foresee the confluence of ‘omics, electronic health records, and artificial intelligence coming together to shape things?

These trends will reboot the practice of medicine in the long term. Deep phenotyping for each individual will enable us to set up more precise, effective and safe care. We’ll be able to achieve prevention for the individual's conditions known to be putting her/him at risk. And the use of the virtual health coach that integrates all of a person’s data for improving self-care. I spent a lot of time researching these topics for my book, Deep Medicine.

Finally, at ISPOR our focus is on value in healthcare delivery, what are your thoughts on current approaches to health technology assessment?

We desperately need validation and replication in diverse participants and at scale, along with follow-on studies after implementation to corroborate the initial hypotheses and findings. We’re currently not using the technology that is available enough—we can harness it all to do these studies efficiently and seamlessly.

To learn more about the Scripps Institute Translation Institute and the progress being made in human genomics, go to https://www.scripps.edu/science-and-medicine/translational-institute/
Announcing the spring issue of The Evidence Forum

Focus on Rare Diseases

- Key takeaways from FDA’s updated guidance
- Patient engagement and COAs
- Natural history studies and genetic markers
- Payer perspectives and early scientific advice
- And much more on evidence needs for rare disease treatments

evidera.com