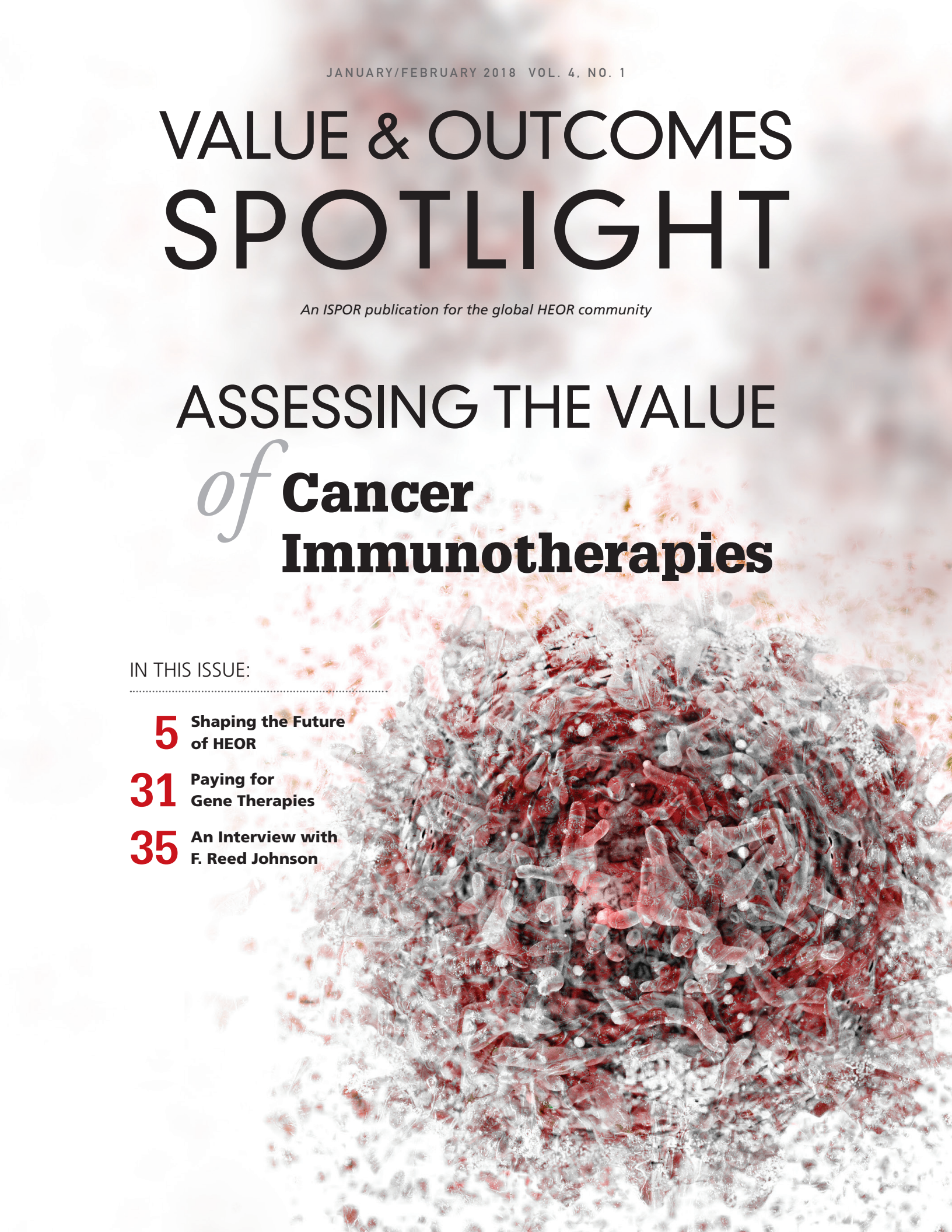
JANUARY/FEBRUARY 2018 VOL. 4, NO. 1

VALUE & OUTCOMES SPOTLIGHT

An ISPOR publication for the global HEOR community

ASSESSING THE VALUE *of* Cancer Immunotherapies



IN THIS ISSUE:

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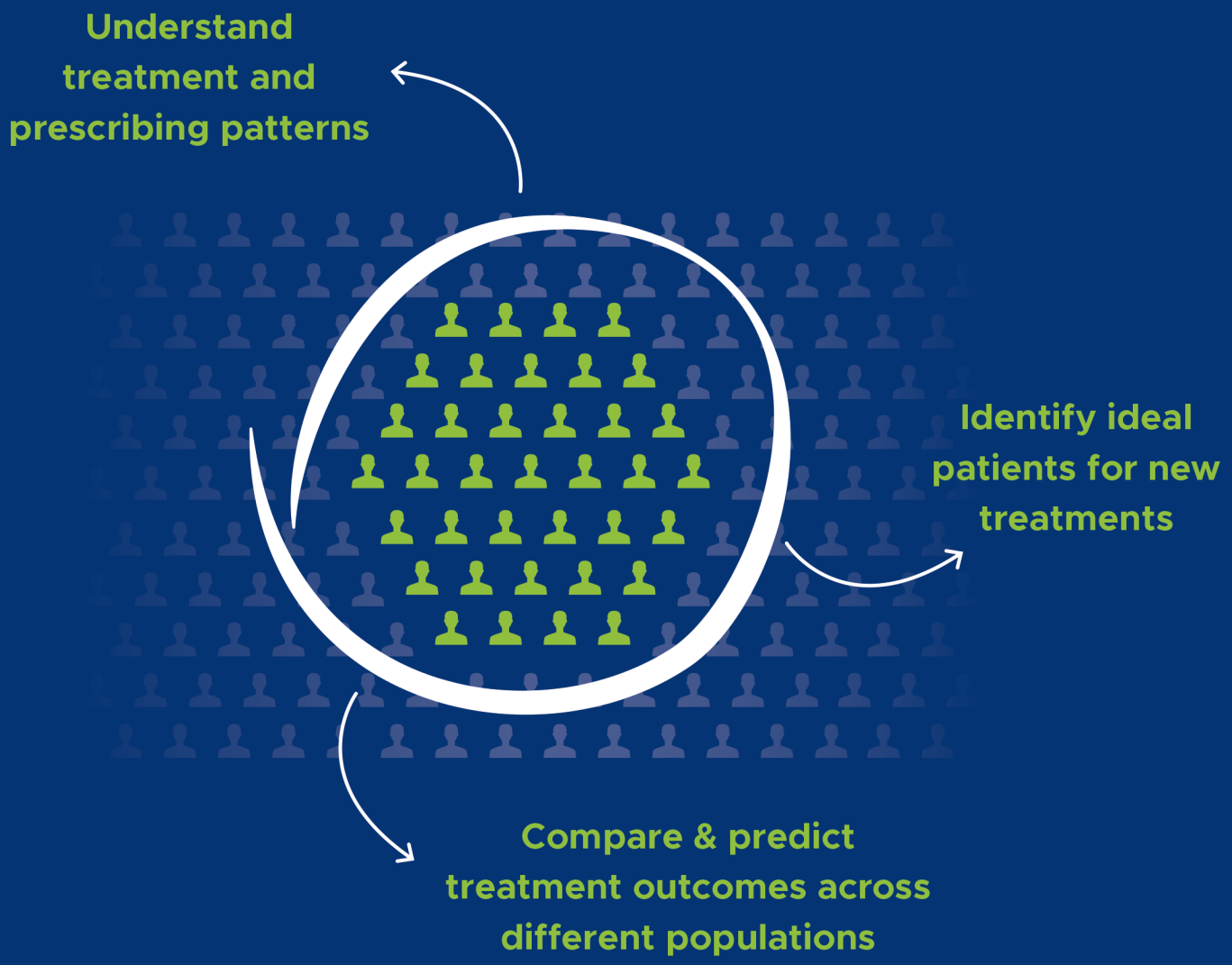

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VALUE & OUTCOMES
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JANUARY/FEBRUARY 2018
VOL. 4, NO. 1

Table of Contents

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

ISPOR
Improving healthcare decisions

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FROM THE EDITOR

It is typical at this time of year for people to pursue their New Year's Resolutions, the most common of which include eating healthier, getting more exercise, and saving more money. Surveys suggest that most people will fail to sustain these changes for more than a month or so, but the main point is that this is a good time to consider constructive improvements.

This is true too for *Value & Outcomes Spotlight*, which has now entered its fourth year of existence. We are continually looking to evolve to better serve ISPOR members and others interested in formally bringing value considerations to healthcare decisions. The publication strives to do so in an accessible format that encompasses important news, key methodologic issues, and policy issues of relevance to our community.

In reviewing this issue you will likely notice the changes to its look and feel compared with previous issues—more graphics, larger pictures, and a magazine-like format. Indeed, we no longer refer to *Spotlight* as a 'journal' and this will further help extricate it from the shadow of ISPOR's highly successful peer-reviewed journal, *Value in Health*, and its offspring, *Value in Health Regional Issues*.

But the evolution of *Value & Outcomes Spotlight* goes beyond mere formatting. We are introducing a new section, entitled "ISPOR Central," which begins with a piece authored by a member of ISPOR's executive leadership (in the current issue, ISPOR's CEO Nancy Berg), followed by a capsule summary of relevant HEOR news items, a roundup of research from the peer-reviewed literature, a listing of conferences and events of relevance to ISPOR members, and finally an overview of forthcoming articles in *Value in Health*.

Also, for the first time, we have identified in advance content themes for each of the six issues that will be released this year and we have proactively developed or solicited articles surrounding each issue theme. The current issue's theme is cancer immunotherapy and you'll find interesting articles on how to assess the value of immuno-oncology drugs, caveats for data analysis and choice of statistical methodology for comparative analyses of immuno-oncologic versus traditional cytotoxic regimens, and implications for assessment of patient-reported outcomes for patients receiving personalized oncology treatments. Certainly the tremendous potential of these drugs sits alongside their tremendous costs, which amplifies the need for a careful analysis of value for money.

We hope you believe as we do that *Value & Outcomes Spotlight* is becoming more relevant and useful to our Society and beyond. As always, we welcome your feedback and suggestions.

Thank you for your interest in the publication!

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

ISPOR SPEAKS

A Look Ahead: ISPOR's Role in Shaping the Future of HEOR

Nancy S. Berg, CEO & Executive Director

The start of a new year provides opportunity to communicate with members about how your Society is leading to improve healthcare decision making worldwide. Healthcare reform is underway in nearly every corner of the globe. Unprecedented advancements are taking place in drug development and medical interventions, populations are aging, and costs are on the rise. Add to that debates over the definition of value continue to rage and advances in methods and evaluation techniques that are at our fingertips. In the blink of an eye, technology is driving change; market access, health technology assessment, and decision making are under closer scrutiny than ever before…and I could go on. These realities and trends—although some seem insurmountable—clearly place health economics and outcomes research (HEOR) and ISPOR at the epicenter of critical conversations and decisions—and at the cutting edge of a critically important sector of the healthcare field. This is an exciting time for ISPOR. So, how are we responding?

> As the leading professional Society in the field, ISPOR is uniquely positioned to leverage the thought leadership of its members to provide direction on where the HEOR field is heading.

Leveraging the expertise and long-term experience of our members, ISPOR will continue to address important issues in healthcare and drive new initiatives to advance the understanding and application of HEOR methodologies in healthcare decisions. Some of the major themes that ISPOR will address in 2018 and feature at our Baltimore meeting (May 19-23, 2018) include further discussion on **patient-centered research and measuring patient-reported outcomes**, continued examination of the role and appropriate use of **real-world evidence**, and an ongoing assessment of ever-evolving advances in **new technologies** (eg, digital and mHealth). These themes, among many others, are highlighted to help members and decision makers remain on the cutting edge.

As the leading professional Society in the field, ISPOR is uniquely positioned to leverage the thought leadership of its members to provide direction on where the HEOR field is heading.

- For example, ISPOR will continue to solidify its role as a resource for health policy through the newly restructured Health Science Policy Council. We understand that a major part of our role as a Society is information dissemination not just to members, but also to payers, governments, and other decision makers who benefit from the understanding and use of HEOR tools and methodologies.
- Our leadership commitment also includes an ongoing effort to respond to public calls for comment to ensure the voice of ISPOR members is conveyed to governments and regulators who seek input from various stakeholders as they advance and reform their systems.
- Similarly, the ISPOR 2018 Top HEOR Trends inaugural report was released in January to provide an overview of the topics that will be driving healthcare discussions in the coming months and years.

As part of our Strategic Plan, ISPOR developed a comprehensive approach for engaging with other professional, trade, and government organizations. More than 40 societies, associations, and groups are identified in our plan, along with Ministries of Health, HTA agencies, regulators, payers, and other decision makers. We believe open dialog is critical to advancement of ISPOR's mission, and we value input of other groups in our programs and plans. A key 2018 collaboration strategy is to increase communication with clinicians, and we have begun meeting with clinical groups in oncology, cardiology, and neurology to better understand how ISPOR can support these organizations and their members. This outreach often results in collaboration such as the recent participation of ECCO's (European Cancer Organisation) president in a plenary session at our European Congress in Glasgow and the joint papers on real-world evidence produced with ISPE (International Society for Pharmacoepidemiology) last year.

In 2018, the formation of the new ISPOR Patient Council will build on important conversations among patient representatives and researchers. ISPOR Patient Roundtables operating in Europe, Latin America, and North America (and later this year, in Asia-Pacific) will contribute to ISPOR strategies and gain access to the research community to learn, share, and advance their objectives.

Looking at 2018 and beyond, it is clear that through our collective efforts we are building a better ISPOR. ISPOR is leading at a time when solid approaches to decision making are more important than ever. I encourage each of you to get involved in your Society—be present at a "must-attend" ISPOR conference, volunteer to be a peer reviewer for our MEDLINE-indexed journals, join a group, and encourage your colleagues to become members. Together we will continue to make important contributions that move the field forward.

HEOR NEWS

A diverse collection of relevant news briefs from the global HEOR (health economics and outcomes research) community.

1 NICE backs interim funding for Janssen cancer drug (pharmaphorum)

After months of wrangling, the National Institute for Health and Care Excellence (NICE) has recommended that Janssen's Darzalex (daratumumab) should be reimbursed on an interim basis by the Cancer Drugs Fund (CDF) in pre-treated multiple myeloma. In a separate decision, NICE has asked Pfizer to submit a proposal to the CDF for funding for its product Xalkori (crizotinib) in certain patients with lung cancer. Last March, NICE rejected Darzalex in its use in its third-line multiple myeloma use, although Janssen asked for it to be funded as a fourth-line treatment where it is likely to be most effective.

https://pharmaphorum.com/news/nice-backs-interim-funding-janssen-cancer-drug/

2 Seizing opportunities in the next steps for real-world evidence (Pharmafile)

Efficacy data is what drives the pharmaceutical, medical, and healthcare industries and beyond. Alongside safety data, it is the key arbiter of a medicine's effectiveness in its primary purpose in the world, and is the essential commodity that clinicians and other professionals trade in. And the vehicle that delivers this commodity is, of course, the clinical trial, which has reliably generated such data through, in the best circumstances, carefully constructed studies based on sound science with a wide and representative participant population. But, in today's climate where efficacy and safety of healthcare treatments are increasingly scrutinized, is this traditional process and dataset enough to achieve the highest standards that we expect? There is a consensus in the industry that the answer to many of the problems that arise from this methodology can be found in real-world data, and the real-world evidence which can be drawn from them. This was one of the center points of the seminar 'Realizing the potential of real-world evidence' at the recent Global Pharmaceutical and Biotechnology Conference held by the Financial Times in London, where key figures from the field came together to discuss their experience of real-world data and real-world evidence and how they felt stakeholders could capitalize on their benefits moving forward.

http://www.pharmafile.com/news/516261/seizing-opportunities-next-steps-real-world-evidence?utm_source=NPC+Contact+List&utm_campaign=d1195d1759-EMAIL_CAMPAIGN_2018_01_16&utm_medium=email&utm_term=0_3ddd3927eb-d1195d1759-198281001

3 German watchdog calls for direct comparison of cancer immunotherapies (Reuters Health/PharmaLive)

Germany's drug assessment body has criticized a lack of data directly comparing drugs in a promising new class of cancer immunotherapies, saying physicians could be overwhelmed or misled by the available information. IQWiG, the independent authority in Germany that evaluates new drugs and plays a key role in establishing what price health services pay for them, has looked into new immunotherapy drugs for the treatment of bladder cancer as part of its so-called early benefit assessment. It concluded there were some signs that patients who could not be helped by previous courses of standard chemotherapy could benefit considerably from Merck & Co's Keytruda (pembrolizumab) and Roche's Tecentriq (atezolizumab), but said physicians needed head-to-head trials to pick the best treatment option.

http://www.pharmalive.com/german-watchdog-calls-for-direct-comparison-of-cancer-immunotherapies/

4 7 applications of machine learning in pharma and medicine (TechEmergence)

When it comes to effectiveness of machine learning, more data almost always yields better results—and the healthcare sector is sitting on a data goldmine. McKinsey estimates that big data and machine learning in pharma and medicine could generate a value of up to $100 billion annually, based on better decision making, optimized innovation, improved efficiency of research/clinical trials, and new tool creation for physicians, consumers, insurers, and regulators. Where does all this data come from? If we could look at labeled data streams, we might see research and development; physicians and clinics; patients; caregivers; etc. The array of (at present) disparate origins is part of the issue in synchronizing this information and using it to improve healthcare infrastructure and treatments. Hence, the present-day core issue at the intersection of machine learning and healthcare: finding ways to effectively collect and use many different types of data for better analysis, prevention, and treatment of individuals.

https://www.techemergence.com/machine-learning-in-pharma-medicine/

HEOR NEWS

5 Analyzing behavioral economics and psychology are key to engaging patients to make meaningful changes (HealthcareIT News)

So many well-meaning patient engagement efforts are based on a fallacy. The logical assumption is that by connecting patients with technology—equipping them with access to their personal health data or the educational information relevant to their condition—they will take a more active role in their personal health. But all the portals, pedometers, and Bluetooth-connected scales in the world will only make so much difference—and only on a certain portion of the patient population. "The idea that we should educate people and help them make better decisions has only minimal effectiveness," says David Asch, MD, executive director of Penn Medicine's Center for Health Care Innovation.

http://www.healthcareitnews.com/news/analyzing-behavioral-economics-and-psychology-are-key-engaging-patients-make-meaningful-changes

6 Biogen 'optimistic' for NHS access to Spinraza (PharmaTimes)

Biogen says it is "optimistic" that patients in England and Wales with a rare spinal disorder will get rapid and broad access to Spinraza (nusinersen) via the National Health Service. According to the firm, the National Institute for Health and Care Excellence (NICE) has formally invited the group to submit Spinraza, which it notes is the first and only disease-modifying treatment for the condition, for assessment via the single technology appraisal route.

http://www.pharmatimes.com/news/biogen_optimistic_for_nhs_access_to_spinraza_1218114?utm_content=buffer9c90c&utm_medium=social&utm_source=twitter.com&utm_campaign=buffer

7 UnitedHealth sees a new frontier in Latin America (Forbes)

UnitedHealth Group executives look at Latin America and see the US healthcare market of the early 1990s, before private health insurers were involved much at all in the management of government-subsidized health benefits. Private insurers like UnitedHealth, Aetna, Humana, Cigna, and others began to take a far greater role following the Balanced Budget Act of 1997, which slowed the growth of Medicare spending amid a booming population of aging baby boomers. The budget law and the subsequent move away from fee-for-service Medicare set the stage for what today are known as private Medicare Advantage plans, which contract with the federal government to provide benefits to seniors. By 2003, the Medicare Modernization Act opened the door to Medicare Part D drug benefits admitted by private insurers. More states in the past 20 years have also turned to private administration of Medicaid benefits for poor Americans.

https://www.forbes.com/sites/brucejapsen/2018/01/22/why-unitedhealth-group-sees-a-new-frontier-in-latin-america/#28a073d734cf

8 Cost effectiveness of de-escalation from micafungin versus escalation from fluconazole for invasive candidiasis in China (Journal of Medical Economics)

Guidelines on treating invasive candidiasis recommend initial treatment with a broad-spectrum echinocandin (eg, micafungin), then switching to fluconazole if isolates prove sensitive (de-escalation strategy). This study aimed to evaluate the cost effectiveness of de-escalation from micafungin versus escalation from fluconazole from a Chinese public payers perspective.

http://www.tandfonline.com/doi/abs/10.1080/13696998.2017.1417312?journalCode=ijme20

9 Did the government overpay for hundreds of drugs? It's complicated (STAT)

It looked like the watchdog had found something big—in December 2017, a government report proclaimed that drug companies might have stiffed Medicaid over a billion dollars by pricing some brand-name drugs like generics. The report didn't name those companies, but Mylan, maker of EpiPen, landed in hot water for similar behavior the year before. In August 2017, the company paid a $465 million settlement, facilitated by the Department of Justice, and agreed to have its pricing practices reviewed in order to resolve claims that it overcharged Medicaid for EpiPen. Sen. Chuck Grassley (R-Iowa), one of the lawmakers who requested the report, immediately called on Medicaid to recoup the funds. And earlier this month, Alex Azar, the nominee to lead the Department of Health and Human Services, said that he was "very concerned" about the situation.

https://www.statnews.com/2018/01/22/medicaid-drug-payments/

10 How well can you predict the outcome of clinical trials? Not as well as you may think (STAT)

If researchers were better at forecasting the results of clinical trials—and, say, could avoid having to run trials that will inevitably fail—more resources could be devoted to trials that might succeed. But, it turns out, researchers might not be great at determining the likelihood of a trial's success. In unpublished research, McGill bioethicist Jonathan Kimmelman and colleagues asked cancer experts to forecast the probability of more than a dozen clinical trials hitting their primary endpoint. They found that the predictions overall were not very accurate, and, if anything, were too pessimistic.

https://www.statnews.com/2018/01/22/clinical-trials-forecasting-outcomes/

RESEARCH ROUNDUP

Section Editors: **Gabriela Tannus Branco de Araujo, MSc** and **Marcelo Fonseca, MD, MSc**

New drugs, new toxicities: severe side effects of modern targeted and immunotherapy of cancer and their management

Author and publication information: Kroschinsky F, Stolzel F, von Bonin S, Beutel G, Kochanek M, Kiehl M, Schellongowski P; Intensive Care in Hematological and Oncological Patients (iCHOP) Collaboration Group. Crit Care. 2017; 21(1):89

Summary: Antibody treatments may lead to immunity-related adverse events and may lead to hospitalization of patients in intensive care units, especially those linked with respiratory infections. This article examines several focused meta-analyses on the toxicities related with new immuno-oncology therapies.

Relevance: This study reinforces the need for a consistent evaluation not only of the positive results of the new treatments, but also of the adverse events related to these immuno-oncology treatments.

Economic health assessments take into account the positive and negative consequences of new treatments. Thus, consideration of adverse events and their respective costs are an important point in the evaluation process. The severity and/or the appearance of new adverse events can have a great initial economic impact, since the teams that accompany the patients may present a learning curve for the handling of occurrences that previously did not happen, were less frequent, or even less serious.

For the health economics and outcomes research field, this article may represent an important alert for researchers to take the necessary steps and precautions in their assessments, considering this key issue. It is important not only to value the beneficial results of immuno-oncology treatments, but also their new profile of adverse events and the composition of their associated costs.

Value frameworks for the patient-provider interaction: a comparison of the ASCO value framework versus NCCN evidence blocks in determining value in oncology

Author and publication information: Shah-Manek B, Galanto JS, Nguyen H, Ignoffo R. J Manag Care Spec Pharm. 2017;23(6-a Suppl):S13-S20.

Summary: The article compares two different frameworks, the ASCO Value Framework and the NCCN Evidence Blocks, to evaluate oncologic treatments.

The ASCO Value Framework compares 2 treatments that have been studied through a prospective randomized clinical trial, generating a net health benefit outcome and comparing the cost of purchasing drugs from each regimen, providing a summary score for treatments in all categories of clinical benefit and toxicity.

The National Comprehensive Cancer Network Evidence Blocks represents average values provided by a group of experts in an array, assessing and assigning points related to treatment efficacy, safety, quality, consistency of evidence, and accessibility.

Relevance: The frameworks presented very different results, which can be explained by the difference in the nature of these evaluations. The authors emphasized that both tools are new and present challenges in their use and in their goals. As immuno-oncology treatments will be challenged by these and other decision-making frameworks, the validity of the measured outcomes must be analyzed and tested in order to reflect the real treatment value.

Considering all the discussion around the use, validity, and applicability of these and other frameworks, this is a key issue for health economics and outcomes researchers and decision makers.

RESEARCH ROUNDUP

The changing face of clinical trials in the personalized medicine and immuno-oncology era: report from the International Congress on Clinical Trials in Oncology & Hemato-Oncology (ICTO 2017)

Author and publication information: Golan T, Milella M, Ackerstein A, Berger R. J Exp Clin Cancer Res. 2017; 28(1):192.

Summary: The article describes the challenges regarding the design and selection of outcomes (such as the inclusion of patients' perspectives regarding treatment) in clinical studies that evaluate immuno-oncology and biomarker-oriented drugs.

This is a report on the discussions that happened during the International Congress on Clinical Trials in Oncology and Hemato-Oncology (ICTO2017).

Relevance: Design changes, changes in the selection of outcomes, and the inclusion of patients' perspectives would certainly have a major impact on economic evaluations. In addition, these changes would also affect how decision makers might have to prepare themselves to understand and evaluate the importance and impact of these outcomes on patients' lives and health investment in oncology.

Modelling the survival outcomes of immuno-oncology drugs in economic evaluations: a systematic approach to data analysis and extrapolation

Author and publication information: Gibson E, Koblbauer I, Begum N, Dranitsaris G, Liew D, McEwan P, Tahami Monfared AA, Yuan Y, Juarez-Garcia A, Tyas D, Lees M. Pharmacoeconomics. 2017; 35(12):1257–1270.

Summary: The objective of this article was to discuss the change of the current pattern of results evaluation to construct the survival curves by a new one. This new pattern would more accurately demonstrate the results of new immuno-oncology therapies.

Survival curves are the heart and soul of economic models in oncology. Through these curves, we can estimate the progression-free survival differences and specially the difference in overall survival between available therapies.

One of the main points discussed in this article is the use of the Responsive Evaluation Criteria in Solid Tumors (RECIST) as a marker for evaluation of tumor reduction. Considering that the treatments in immuno-oncology initially provoke an enlargement of the tumor, the use of RESIST as marker could underestimate its results.

The article presents a not yet fully adopted, new marker called immune-related response criteria (irRECIST). For irRECIST, response standards take into account changes in all lesions (not just target lesions [with new lesions not considered progressive disease per se] and thresholds that determine progression or response) are higher than those specified by RECIST.

Relevance: As many economic analyzes continue to be performed using the traditional methods, these analyzes may be failing to extrapolate survival curves and consequently, failing to adequately assess the results of immuno-oncology.

The article proposes a model called spline-based, which would be more appropriate to assess and capture the value of immune-oncology therapies. In this model, described as more flexible, there would be a minimization of subjectivity and uncertainty around the premises necessary for evaluations that are more complex.

NOTE: The preceding items are simplified summaries of the published articles. They do not represent an opinion or an in-depth analysis on the results. The selection of these works was made based on theme relevance, not a product of a literature review or of a methodological quality selection.

MARK YOUR CALENDAR FOR ISPOR'S 2018 EVENTS!

- **Essential Elements of Pricing**
  March 20-21, 2018
  Durham, NC, USA

- **Build a Budget Impact Model: Budget Impact Analysis Training**
  March 22-23, 2018
  Durham, NC, USA

- **Patient-Reported Outcomes**
  April 10-11, 2018
  Durham, NC, USA

- **Introduction to HEOR**
  April 12-13, 2018
  Durham, NC, USA

- **23rd Annual International Meeting**
  May 19-23, 2018
  Baltimore, MD, USA

  Registration is open!
  Abstract Acceptance Notification: March 1
  Early Registration Deadline: April 10

  Pre-meeting HEOR Short Courses Offered

- **HTA Training Program**
  June 2018
  Philadelphia, PA, USA

HTA Training Program
23-26 July, 2018
Lima, Peru

8th Asia-Pacific Conference
8-11 September 2018
Tokyo, Japan

Abstract Submission Deadline:
14 March
Early Registration Deadline:
17 July

Pre-meeting HEOR Short Courses Offered

Regional Meeting
19-20 September 2018
Dubai, United Arab Emirates

Early Registration Deadline:
7 August

21st Annual European Congress
10-14 November 2018
Barcelona, Spain

Abstract Submission Opens:
1 March
Abstract Submission Deadline:
13 June
Early Registration Deadline:
25 September

Pre-meeting HEOR Short Courses Offered

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Who

Anyone who is conducting health economics and outcomes research (HEOR) to inform healthcare decisions is encouraged to submit content for consideration.

What

Conference content can be submitted in the following categories:

RESEARCH ABSTRACTS:
Outcomes research on all healthcare interventions, diseases, or methodologies are considered.

ISSUE PANEL PROPOSALS:
Issue panel presentations are designed to show a real debate or discuss multistakeholder perspectives on a new or controversial issue in HEOR or its use in healthcare decision making.

WORKSHOP PROPOSALS:
Workshop presentations discuss new and innovative applications in the conduct and use of HEOR, real-world data, healthcare policy, and clinical-, economic-, patient-reported, or patient-preference outcomes.

When

See pages 10-11 for a list of upcoming ISPOR conferences.

Where

See pages 10-11 for the locations of upcoming ISPOR conferences.

Why

As the leading professional society for health economics and outcomes research, ISPOR conferences attract a multistakeholder group that is invested in using science and research to make better healthcare decisions. Reap the benefits of presenting your work and networking with this influential audience, and extend your reach and impact by publishing in ISPOR's MEDLINE®-indexed journal (all presented research abstracts are published in *Value in Health*.)

How

For more information on abstract submissions, including instructions, examples, and specific evaluation criteria, please visit www.ispor.org

CONFERENCES & EDUCATION

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As the leading professional society for health economics and outcomes research, ISPOR conferences attract a multistakeholder group that is invested in using science and research to make better healthcare decisions.

Partnering with ISPOR provides a perfect opportunity to meet, network, and collaborate with this influential audience of healthcare decision makers, regulators, payers, researchers, and patient representatives. There are many ways and several venues (see pages 10-11) to begin or expand your partnership with ISPOR:

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PROGRESS THROUGH PARTNERSHIPS—IMPROVING HEALTHCARE DECISIONS TOGETHER.

ISPOR 2018: Do More and B'More in Baltimore!

Rachael L. Fleurence, PhD, National Evaluation System for Health Technology Coordinating Center, Arlington, VA, USA;
C. Daniel Mullins, PhD, University of Maryland School of Pharmacy, Baltimore, MD, USA

Dear Colleagues and Friends,

We are very pleased to welcome you to Baltimore for ISPOR's 23rd Annual International Meeting. Given enormous change in the US healthcare landscape, this year's theme *Real-World Evidence, Digital Health, and the New Landscape for Health Decision Making* is especially timely. Advances in health information technology and personalized data capture (combined with transformation in health insurance, payment, and delivery systems) raise vital questions that will be critically addressed throughout the meeting.

The first plenary *Inflection Point for Real-World Evidence? The Transformational Role of Digital Health* (Monday, May 21) will examine whether we are ready to deliver on the promises of real-world evidence and digital health. The second plenary *Digital Health—Help or Hype?* (Tuesday, May 22) will provide a balanced overview of where there is reliable evidence that digital technologies have improved health and where there is mainly hype. The final plenary (Wednesday, May 23) will focus on stated-preference research and when patients' views on benefit-risk tradeoffs for medical therapies can be useful to inform regulatory decisions.

These plenaries, along with our outstanding short course program, topical issue panels, workshops, and research presentations provide many good reasons to attend. So, too, does the venue, and we are delighted and honored to co-chair the 23rd Annual International Meeting, which returns to Baltimore after 7 years away.

During colonial times, Baltimore was one of the nation's most populated cities because of its port. Today, Baltimore residents refer to the city as "Smalltimore," a nickname that refers to both Baltimore's size and the fact that everyone seems to know one another. Baltimore's Inner Harbor is a vibrant tourist attraction, yet there are a few signs (literally) that are reminiscent of its former stature as a port city, (eg, the iconic Domino Sugars sign.) Baltimore has many famous (and some infamous) celebrities that called "Charm City" their home. One of the most notable is the poet Edgar Allan Poe, who is buried in the graveyard at Westminster Hall, just a 5 minute walk from the ISPOR convention hotel. Poe's legendary impact today is reflected in the fact that the name of the 2-time Super Bowl champion football team is dubbed "The Ravens," named after Poe's iconic poem. Other Baltimore celebrities include baseball player Cal Ripken Jr, and film director John Waters, whose "Hairspray" film reminds its viewers of the once-popular beehive hairdo as well as historical figures like Frederick Douglass and Harriet Tubman. Baltimore was also the location for the iconic TV series "The Wire."

While strolling through the Inner Harbor, check out Miss Shirley's Café for breakfast (warning: no reservations are accepted, so you might have a wait to get a table), The Rusty Scupper for lunch or dinner (the best crab cake restaurant, but also try their cream of crab soup!), the National Aquarium or the Science Center for family fun, or the Reginald F. Lewis Museum of Maryland African American History & Culture for an American history lesson.

We look forward to meeting with all of you to rededicate ourselves to our society that is advancing the science of health economics and outcomes research to improve healthcare decisions.

See you in Baltimore, Hon (that's how we greet you in B'More)!

CONFERENCES & EDUCATION

2017: Year in Review

Investing in the Future

$1.6 million
Reinvested in member programs

Membership

20,000
Individual & chapter members

102
Student chapters

91
Regional chapters

15
New chapters

*Conferences**

10,355
Registrants*

120
Countries represented

193
Exhibitors & sponsors

4979
Presentations

*Totals are from all 2017 ISPOR meetings: Boston, São Paulo, Washington, DC, Glasgow

HEOR Education

5215
Course registrations

61
Course topics

7
New short courses

4
New training programs

Publications: Value in Health

4.235
impact factor

3rd of 77
Health policy journals

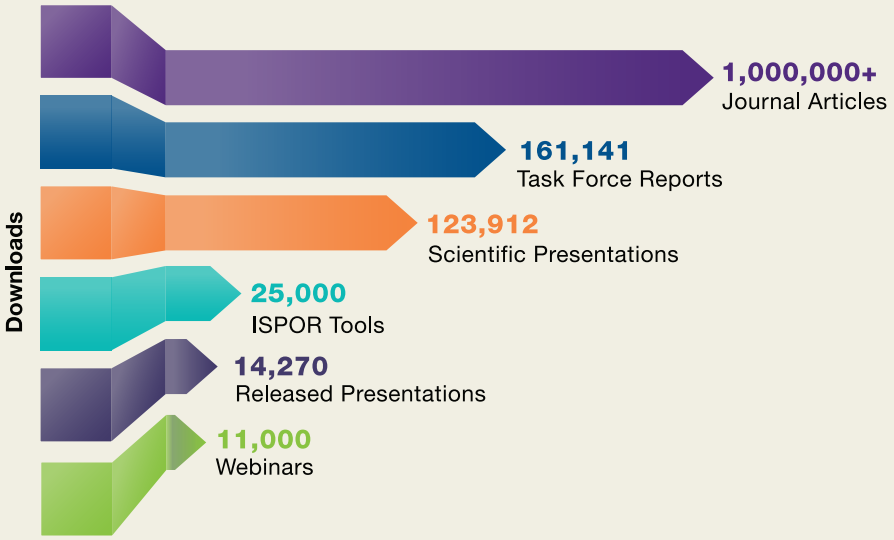
7th of 347
Economics journals

8th of 90
Healthcare science journals

Special Initiatives

Women in HEOR
Real-World Value Evidence Assessment Frameworks

Engagement



FROM THE JOURNALS

The following Editors' Choice articles appear in the January and February 2018 issues of *Value in Health.*

For more information, visit: www.ispor.org/valuehealth_index.asp.

January 2018

COMPARATIVE EFFECTIVENESS RESEARCH / HTA

Comparison of Adalimumab and Etanercept for the Treatment of Moderate-to-Severe Psoriasis: An Indirect Comparison using Individual Patient Data from Randomized Trials

Yang M, Papp KA, Sundaram M, et al.

In this article, the authors compare outcomes between adalimumab and etanercept in the treatment of moderate-to-severe plaque psoriasis.

HEALTH POLICY ANALYSIS

Payer and Pharmaceutical Manufacturer Considerations for Outcomes-Based Agreements in the United States

Brown JD, Sheer R, Pasquale M, et al.

This analysis builds hypothetical OBA models where both payer and manufacturer can benefit.

PREFERENCE-BASED ASSESSMENTS

EQ-5D-5L versus 3L: The Impact on Cost Effectiveness in the UK

Wailoo A, Hernandez M, Grimm S, et al.

The authors model the relationship between EQ-5D-3L and EQ-5D-5L and examine how differences impact on cost effectiveness in case studies.

METHODOLOGY

Accounting for Uncertainty in Decision Analytic Models Using Rank Preserving Structural Failure Time Modeling: Application to Parametric Survival Models

Bennett I, Paracha N, Abrams K, Ray J

The aim of the study is to describe novel approaches to adequately account for uncertainty when using a RPSFT model in a decision analytic model.

February 2018

THEMED SECTION: US VALUE ASSESSMENT FRAMEWORKS

The February 2018 issue features a special section of papers reporting on the work of ISPOR's Special Task Force on US Value Assessment Frameworks. The collection includes an introductory editorial, 7 task force reports, and 4 commentaries that provide valuable insights from the payer, patient, academic, and industry perspectives.

EDITORIAL

A Health Economics Approach to US Value Frameworks: Serving the Needs of Decision Making

Norman R, Chalkidou K, Culyer A

ISPOR REPORTS

A Health Economics Approach to US Value Assessment Frameworks—Introduction: An ISPOR Special Task Force Report

Neumann PJ, Willke RJ, Garrison LP

An Overview of Value, Perspective, and Decision Context—A Health Economics Approach: An ISPOR Special Task Force Report

Garrison LP, Pauly MV, Willke RJ, Neumann PJ

Defining Elements of Value in healthcare—A Health Economics Approach: An ISPOR Special Task Force Report

Lakdawalla DN, Doshi JA, Garrison LP, Phelps CE, Basu A, Danzon PM

Objectives, Budgets, Thresholds, and Opportunity Costs—A Health Economics Approach: An ISPOR Special Task Force Report

Danzon PM, Drummond MF, Towse A, Pauly MV

Approaches to Aggregation and Decision Making—A Health Economics Approach: An ISPOR Special Task Force Report

Phelps CE, Lakdawalla DN, Basu A, Drummond MF, Towse A, Danzon PM

Review of Recent US Value Frameworks— A Health Economics Approach: An ISPOR Special Task Force Report

Willke RJ, Neumann PJ, Garrison LP, Ramsey SD

A Health Economics Approach to US Value Assessment Frameworks—Summary and Recommendations of the ISPOR Special Task Force Report

Garrison LP, Neumann PJ, Willke RJ, et al.

COMMENTARIES

ISPOR's Initiative on US Value Assessment Frameworks: The Use of Cost-Effectiveness Research in Decision Making Among US Insurers

Pezalla EJ, Solow B

ISPOR's Initiative on US Value Assessment Frameworks: A Missed Opportunity for ISPOR and Patients

Perfetto E

ISPOR's Initiative on US Value Assessment Frameworks: Seeking a Role for Health Economics

Sculpher M

ISPOR's Initiative on US Value Assessment Frameworks: An Industry Perspective

Dougherty S, Burkholder R, Neves L

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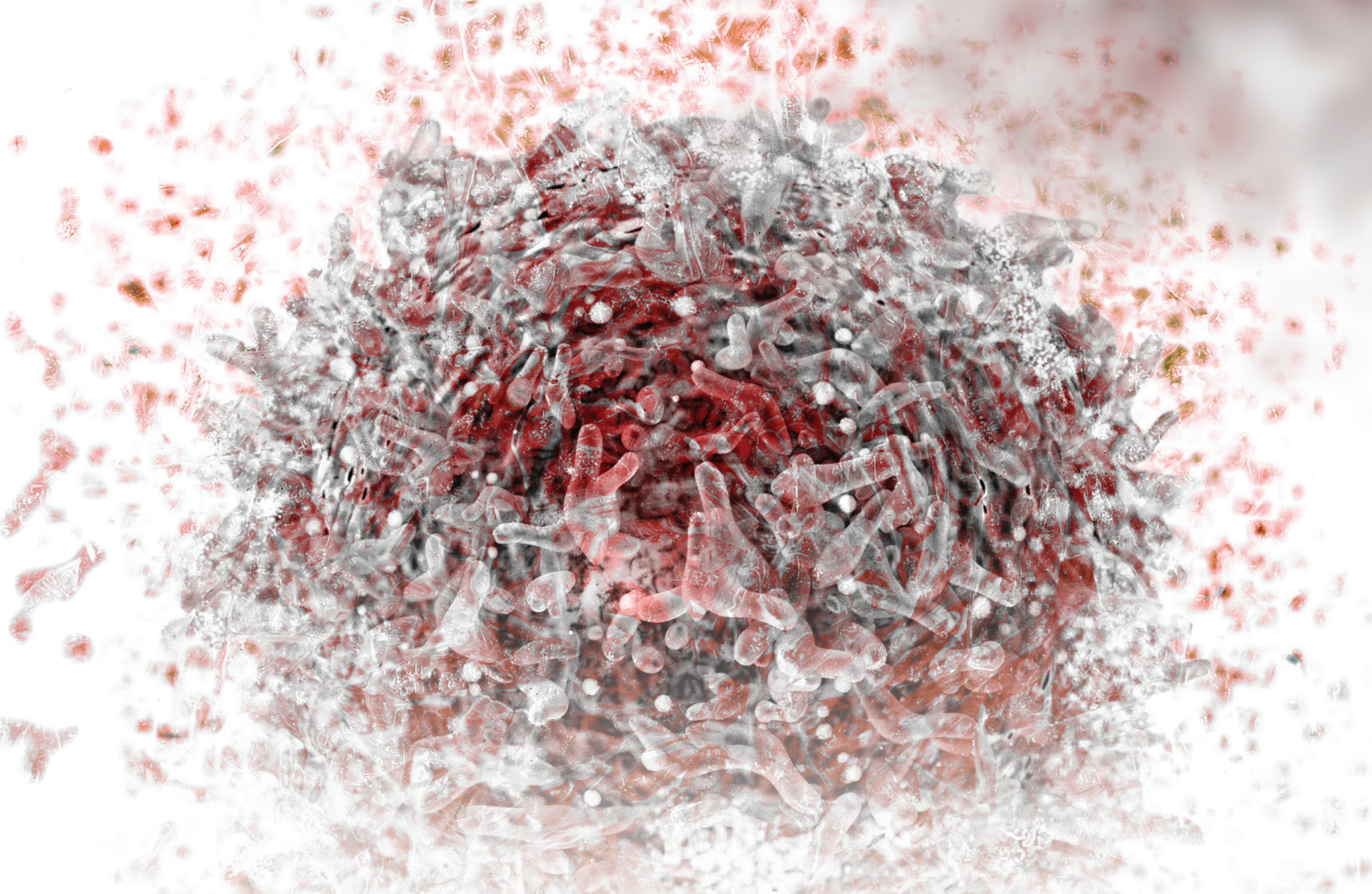


ASSESSING THE VALUE *of* Cancer Immunotherapies

By Christiane Truelove

The new classes of cancer immunotherapies hold great, exciting clinical promise across a number of cancer types, with the potential of extending the lives of patients who previously had no options. But these drugs also come with an eye-watering sticker price, with courses of treatment costing hundreds of thousands of dollars.

As more indications for already marketed drugs are approved and new drugs come out of the pipeline, payers across the world are grappling with how to evaluate these drugs and deciding whether they are worth the cost of making them available to patients. When the concept of value can vary from country to country, payer to payer, clinical group to clinical group, patient to patient, how can all these viewpoints of value be reconciled? The good news is that ISPOR members strongly believe that there will be a more unified evaluation of the value of cancer immunotherapies, and payers in the United States will catch up with health technology assessment (HTA) bodies around the world.

EUROPEAN VS. US VIEWPOINT

"Most of the United States has a different approach; particularly in the public sector, there are not really any assessments for economics or value," says Michael Drummond, MCom, DPhil, University of York, and one of the Co-Editors in Chief of *Value in Health*. "CMS [Centers for Medicare & Medicaid Services] approves everything in cancer as soon as the FDA [Food and Drug Administration] licenses the drug."

Meanwhile, in Europe, there are 3 general approaches to assessing the value of drugs. One is "kind of like the United States, which is next to nothing," according to Drummond. These countries, predominantly in Southern Europe, do not conduct any assessments beyond what the licensing agency does to grant approval, an approach that he called "sparse."

In central and northern Europe, there are 2 approaches. The more common approach is to assess the incremental costs based on quality-adjusted life year (QALY) and then make a formal or informal judgment about whether the drug gives enough in terms of improved length and quality of life in relation to the cost. The United Kingdom is the most formal in this approach, but the Scandinavian countries, the Netherlands, the Republic of Ireland—all of western and northern Europe—would follow this kind of assessment.

The other approach, particularly in Germany and France, involves assessing clinical value on a scale of 1 to 5. In France, a score of 1 is good and 5 is bad; Germany is the reverse. The clinical grading, Drummond says, assesses how much the drug adds to current therapy. So long as the assessment shows that there is some value, irrespective of how much it is judged to be, the drug is allowed to be paid for and there will be price negotiations. "In France it's a little bit more closely defined than Germany, but in France if you get a score of 1 based on the clinical assessment, you can demand a price basically without any discount. But if you get a 4 or 5, you're going to have to take a discount to get the drug on the market."

In terms of the PD-1 immunotherapies, despite the rigor of the UK approach, the first 2 approved—Bristol-Myers Squibb's Opdivo (nivolumab) and Merck & Co.'s Keytruda (pembrolizumab)—"have pretty much been recommended," Drummond says. "In a couple of cases, depending on the indication, there's been the requirement to give the government some kind of a price cut."

The overall presumption in Europe is that these immunotherapies will work and provide long-term value. In the richer European countries, the drugs have gone through the value assessment and "come out the other side with mostly a positive determination," according to Drummond. "Obviously in the long run, who knows whether these drugs really work, but I think the presumption is that they do."

In the US private sector, while there are a couple of value assessment frameworks (such as those created by American Society of Clinical Oncology [ASCO] and Memorial Sloan Kettering), "in terms of considering value, it's still pretty rudimentary at the moment," Drummond says. The reasons for this are several, including commercial pressures and Medicare's limited negotiating powers.

As the immunotherapy market expands with more drugs and indications for these approved drugs, Drummond expects there will be rebates in the US private sector and deals cut to offer lower prices to certain health plans. "Those rebates are generally confidential but everybody knows that they exist, and I expect that there will be a little bit of price competition."

> As more indications for already marketed drugs are approved and new drugs come out of the pipeline, payers across the world are grappling with how to evaluate these drugs and deciding whether they are worth the cost of making them available to patients.

In both Europe and the United States, there is little pricing transparency for any drug. "In the United Kingdom, you can go on our website for the National Institute of Health and Care Excellence [NICE], and you can look up nivolumab, and it will say that it was recommended for use in an indication, and it might say 'providing that the conditions of the Market Access Agreement are met,' or it might say something like 'providing the commercial arrangements agreed with a company will apply.' This essentially means some kind of to-and fro-ing on price, but all that there is disclosed is that there is an arrangement. In terms of the price cuts, it certainly doesn't say what those price cuts are," Drummond says. "We happen to know in the university because we do evaluations for NICE, we have to put the numbers in to calculate cost effectiveness, so we will know what the price cut is in a given situation but we are not allowed to reveal that."

Discounts offered by the manufacturers, however, will make the price less than the international reference price. "That's what we have to live with right now, but I think one day the international reference price comparison will be out the window, because nobody can believe any prices they see," Drummond says. >

There are also agreements in Europe, particularly the United Kingdom, in which the manufacturer will refund part of the price, get a credit for a future drug, or make another concession if the drug is not shown to work.

In one of nivolumab's indications, for treating locally advanced or metastatic nonsquamous non-small cell lung cancer in adults after chemotherapy, NICE will review how the drug is working after 2 years; if it not working, the patient will have to stop treatment—but refunds are not required. "In other deals, there is a fairly complicated arrangement for what outcomes should be obtained, and if they're not obtained, there could be refunds," Drummond says. "But my understanding with the PD-1s, there haven't been any of those more complex deals. We know if the drug is still working for the patient, the drug is going to deliver, so we can continue."

Drummond says in the future, based on how more countries are looking more intensely at value, he expects US payers to also start looking. "The vacuum left by government is being filled by professional groups and by private plans." In the case of ASCO, the group's concern over value was not about overall cost but of cost to the patient, and patients should be informed because they will have to pick up part of the price of these drugs in copays.

> ISPOR's Initiative on US Value Assessment Frameworks task force is promoting the development and dissemination of high quality, unbiased value assessment frameworks.

The US market is also more complex because some payer groups, in terms of lives insured, are large enough to constitute a European country while others are quite small. "So it's hard for those smaller plans to do the kinds of rigorous assessment that you expect from a payer like the United Kingdom," Drummond says.

The rise of the Institute for Clinical and Economic Review (ICER) in the United States, which did a review of PD-1 inhibitors in lung cancer 18 months ago, has been a particularly interesting development. "It was clear that no one would be trusting the government in the United States to be doing something like that because the level of trust in government is quite low compared to Europe on average," Drummond says. "So ICER's filling the gap, in terms of how all plans can be looking at what they say."

MANUFACTURER'S PERSPECTIVE

Ravinder Dhawan, PhD, Head, Oncology, Center for Observational and Real-world Evidence, Merck, says the hundreds of clinical trials the company is running for Keytruda in multiple tumor indications show, from a value standpoint, "a significant amount of improvement in initial response rates." However, in terms of the drug's true value, it has to show durability of response rates. And he is well aware that not all payers look at value the same way.

"Outside the United States, the HTA agencies will look at the longer view," Dhawan says. "They look at cost effectiveness, they look at the projected survival. They look at how many cost offsets if they put patients on these drugs, what other savings they could have in terms of production and hospitalization. And they allow you to bring all that into the value equation. We can dig in and demonstrate that, and we have a fairly good success with that, with all the HTA agencies."

Meanwhile, in the United States, payers mostly consider the short-term view. "The payers are more focused on one-year budget impact, or maximum two-year budget impact, so they are more keen on show me the activity initially, and then tell me the story of long-term survival or some other point," Dhawan says. "That's the challenge we continue to face, how do you balance that when you have payers looking at value in different ways. But we do one thing that is fairly agreeable and that is we need to continue to collect this long-term data and show the long-term value from a survival standpoint."

Dhawan believes that payer attitudes in the United States are changing, albeit slowly. Part of that is due to the rise of independent groups such as ICER. "There is that natural evolution that's happening in the marketplace, people are starting to look at value from a different perspective, and from a more holistic perspective. ICER is not only looking at value from an outcomes standpoint, but also from a cost effectiveness standpoint. That is going to provide some more perspective about the value and help payers make those decisions."

Although ICER has come under criticism by some manufacturers and patients about how it makes its evaluations, fearing lower payments from government and denial of treatment from insurers, Merck was actually "very pleased" with ICER's evaluation of PD-1 inhibitors in lung cancer. "You could clearly see that the clinical evaluations, the clinical outcomes, the methodologies they used, the analyses they used were pretty sound," Dhawan says. "They were actually in line with what, from Merck's standpoint, we submitted in our submission package to them, and in line with our thinking. Of course, you have to look at the standpoint of a cost per life-year gain, we're pretty much on line with where ICER was. It's only when you start to look at some of the quality of life data and cost per QALY numbers that we started to have some methodological differences. But cost per life-year gained, if that is the measure that payers can use to determine value, that is something that the manufacturers and ICER and the payers can collectively look at and utilize."

One thing is clear, Dhawan says—the ways that value is measured have to evolve. "Everyone is talking about how the evaluation of value cannot be just focused on the narrow ways of looking at the effectiveness and safety and patient-reported outcomes, it has to be more holistic," he says. "And I think there's a big conundrum."

ISPOR's Initiative on US Value Assessment Frameworks task force is promoting the development and dissemination of high quality, unbiased value assessment frameworks. The task force has released a draft white paper with recommendations such as building upon cost-effectiveness analysis; applying cost-effectiveness analysis to inform public and private coverage and reimbursement decision making; managing budget constraints and affordability; and encouraging users of alternative value assessment to gauge their usefulness in terms of consistency, reliability, and fairness in the broader context of healthcare decision making.

"The evolution is going to continue and people are going to form a methodological standpoint to bring different aspects and find ways to not only bring the patient-reported outcomes data along with safety or efficacy, but also a more softer way of looking at patient-centric data and symptom improvement. And also start to look at different perspectives—whether it's a societal perspective, or a payer perspective, or it's a physician perspective, or a patient perspective—different definitions of value," Dhawan says." I think we are headed in the right direction, as slowly, payers are bringing different points of view into the value calculation, and we'll find a way to assimilate all of that."

MEANWHILE, IN JAPAN

Japan's Ministry of Health, Labor, and Welfare uses 3 factors to evaluate a drug for approval: safety, quality, and efficacy. Japan has had sophisticated HTA systems at both the micro and macro levels since 1961, when universal healthcare was first introduced in Asia. Approval, reimbursement, and pricing for new technology (drugs and devices) is all controlled and determined based on rules from Ministry of Health, Labour and Welfare (MHLW), according to Isao Kamae, MD, DhPh, professor of pharmacoeconomics in Japanese Pharmaceutical Manufacturer's Association (JPMA) Project, Keio University, Japan. "The equations for official pricing have been developed in a subjective way, based on political considerations and historical precedent," Kamae says.

Value definition and determination in Japan is a mixture of political and scientific approaches, with "Japanese-style value-based pricing," Kamae says. Once the price is determined, the new technology is subject to be listed on the National Formulary for reimbursement unless the company withdraws. Re-pricing is done biennially and the discounting rate is determined by MHLW, with a constant reimbursement rate of 70% applied automatically for all technologies after first being listed. The manufacturer defines the position of a new drug in multi-outcomes according to the value of the drug, with the government asking developers to define "clinical" value. This value includes quality of life for patients, as well as implicitly defining the drug's broader social benefit. Value for money was implicitly determined until March 2016, when an explicit measure such as cost/QALY was officially used. In April 2016, MHLW introduced a pilot appraisal of cost effectiveness for 7 existing drugs and 6 devices, in response to public concerns about high-cost drugs and devices. This program will be fully implemented and extended to new drugs and devices in 2019 or later, Kamae says.

When it comes to the new cancer immunotherapies, valuation and pricing depends on certain factors that actually apply to every drug approved. Keytruda was approved one year ago in Japan, and therefore has another year to go before its pricing is reconsidered under MHLW rules. But Opdivo (nivolumals), which was the first PD-1 to come to market in Japan in September 2014, has undergone repricing. In the case of Opdivo, a special discount rule was applied. This rule is invoked if a new drug attained a large amount of sales larger than expected at the approval. "We call it market extension re-pricing, which is one of the cost-control mechanisms in Japan," Kamae says. "So considering the extreme budget impact by Opdivo (more than about $3 billion US per year), MHLW applied the Market Extension Re-pricing rule by having politically changed the method as an emergency response, and the price of Opdivo was discounted by 50%."

"The evaluation whether or not MHLW can control costs by introducing cost-effectiveness requirements is still left for future investigation," Kamae says.

By the Numbers

Section Editor: The ISPOR Student Network*

Cancer Immunotherapy

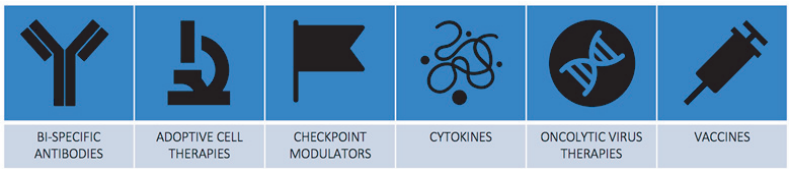
Immunotherapy Timeline

First immuno-oncology treatment was approved for cancer — 1986

2018 — **240+** immuno-oncology treatments in development

Source: www.immunooncology.bmsinformation.com/history-and-research and www.phrma.org/report/list-of-2017-immuno-oncology-medicines-in-development

Classes of Innovation



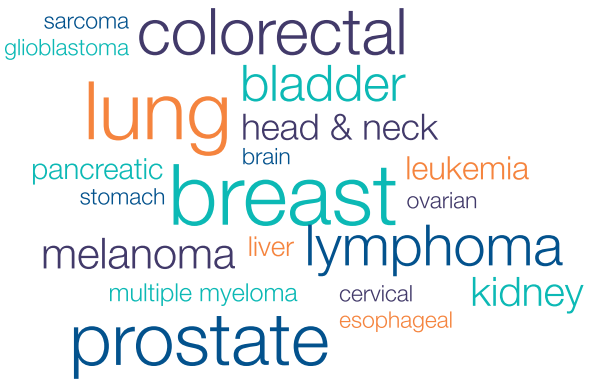
Source: http://catalyst.phrma.org/more-than-240-immuno-oncology-treatments-in-development-to-fight-cancer

Cancer Burden

- More than **100** types of cancers
- **3%** of cancers are caused by viruses
- **1.6** million new cancer cases reported in 2017
- **600,000** cancer deaths expected in 2017

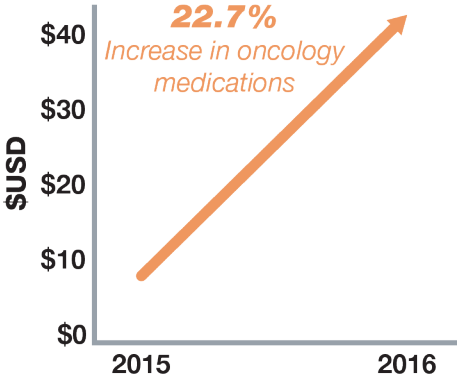
Source: American Cancer Society

20 cancers treated by immunotherapies:

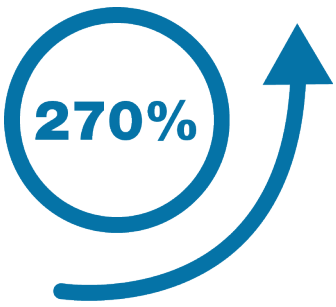


Cost

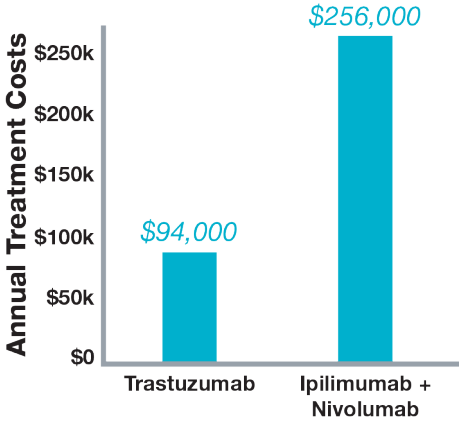
Medicaid Enrollee Costs



Utilization of Immunotherapies



Treatment Costs



Sources: Express Scripts 2016 Drug Trend Report; Pollack A. "FDA Approves a New Drug for Advanced Breast Cancer." *The New York Times*; and Larkin J, Chiarion- Sileni V, Gonzalez R, et al. Combined nivolumab and ilpilimumab or monotherapy in untreated melanoma. *N Engl J Med.* 2015;373(1):23-34

***Contributors:** Omotola Olasupo, University of Florida; Pragya Rai, West Virginia University; Huda Eldabbas, Karan Modi, Mirna Rezkalla, Monica Woloshin, Thomas Jefferson University; Nathaniel Hendrix, Blythe Adamson, Louis Garrison (Chair), University of Washington

Special Considerations for the Analysis of Patient-Level Immuno-Oncology Data

Eric Gemmen, MA, Rockville, MD, USA, and **Louise Parmenter, PhD, MSc**, IQVIA, Real World Insights, Reading, UK

KEY POINTS

Immuno-oncology therapies potentially delayed clinical benefits and durable responses relative to conventional cytotoxic therapy (chemotherapy) mean that study of immuno-oncology therapies require longer term assessment at multiple timepoints to adequately evaluate outcomes.

Real-world and post-marketing studies and patient registries generate evidence to complement that of immuno-oncology clinical trials, given that the strength of immuno-oncology therapy is derived from long-term follow-up.

The potentially delayed response of immuno-oncology therapies suggests that parametric models (exponential, Weibull, piecewise exponential distributions) may be a better fit for analyses of immuno-oncology therapy outcomes than the conventional non-parametric Kaplan-Meier curves and log-rank test.

CANCER IMMUNOTHERAPY

Unlike conventional cancer therapies that directly destroy tumor cells (in addition to healthy cells), immunotherapy drugs for oncology stimulate the patient's own immune system to respond to the cancer in a targeted fashion. These drugs first build a cellular response in the body and then activate tumor regression.

Immunotherapies come in varied types and mechanisms of action:

- Hematopoietic stem cell transplantation
- Checkpoint inhibitors
- Cell-based approaches
- Cancer vaccines

Bladder cancer was the first diagnosis for which immunotherapy became available, with the approval of the BCG (Bacillus Calmette–Guérin) vaccine in 1990. Today, cancers treated by immunotherapy include: bladder, brain, breast, carcinoma, cervical, colorectal, esophageal, gastric, glioblastoma, head & neck, kidney, leukemia, liver, lung, lymphoma, melanoma, multiple myeloma, ovarian, prostate, sarcoma, and skin, among others [1].

EFFECTIVENESS

Assessing whether immuno-oncology therapy helps an individual patient is difficult. Many patients have a potentially delayed response to IO therapy because the treatment does not attack the cancer directly, and one must wait for the immune system to act. It may take several doses of the treatment before seeing an improvement. Some patients even see their cancers worsen before later improving.

When IO therapy does give benefit, sometimes this is substantial, with all cancer spots resolving in the body, leaving no evidence on scans that the cancer remains. This is called a complete response. A partial response is when cancer spots are still visible on the scan but all of them are smaller—a positive outcome as spots left on a scan might simply be scar tissue. So-called stable disease is a third outcome of IO therapy also associated with patient benefit and improved survival. Stable disease means no new spots of cancer, and although the cancer spots are not much smaller, none of them is larger. The reason why this is beneficial in IO therapy is that this stability of IO benefit is often long-lived, and so too is the patient, who can survive for long periods with the cancer clearly visible on the scan. Finally, the fourth outcome of IO therapy is progressive disease, where the drug fails to contain the growing size of the tumor.

> It is unclear if immuno-oncology therapy permanently changes the patient's immune system, but the treatment continues to influence the immune system even after the patient stops receiving it.

Conventional trial designs and endpoints do not capture the novel patterns of IO therapy response and thus afford only a partial view of effectiveness. IO therapy's potentially delayed clinical benefits and durable responses relative to conventional cytotoxic therapy (chemotherapy) mean that study of IO therapies: requires longer-term assessment to evaluate outcomes adequately; requires greater sample size to observe treatment effects, as dropouts over longer duration of follow-up must be anticipated; and requires analyses at multiple time points to understand durability of response, realizing that early interim analyses in the context of delayed effectiveness may signal early false-negative results that are misleading.

SIDE EFFECTS

IO therapy is not like other cancer treatments; it is not chemotherapy. The side effects are very different from those of other cancer treatments because immunotherapy works differently from other therapies. The side effects of IO are related to overstimulation of the immune system, rather than suppression of the immune system like chemotherapy. The most common immune-related adverse >

events include skin (rash, pruritus), gastrointestinal tract (diarrhea, colitis), liver (hepatitis) and endocrine system (hypothyroidism, hypopituitarism, adrenal insufficiency, and hypophysitis) [2,3]. The side effects of IO therapy depend upon the type of therapy (checkpoint inhibition or other) and the individual patient, and they can start as mild issues and worsen very quickly [4].

It is unclear if IO therapy permanently changes the patient's immune system, but the treatment continues to influence the immune system even after the patient stops receiving it. In some cases, patients who are given IO therapy do not show any improvement in their cancer until 6 months after they stop the therapy; and likewise, some patients can develop side effects months after taking IO therapy. This possibility furthers the need for longer-term follow-up in IO research through real-world extension studies of patients from clinical trials and other types of long-term real-world and post-marketing studies.

Real-world and post-marketing studies such as product registries complement IO clinical trials, which may have been shorter than is optimal, given the potentially delayed benefits and side effects of IO therapies. In particular, real-world database analyses and patient registries can follow a larger number of patients for a longer duration of time more easily, which is necessary when the strength of IO therapy is derived from long-term follow-up. A further need for research is to better understand the power of short-term, interim, surrogate endpoints (eg, elimination of antigens, T-cell response) in predicting longer-term outcomes such as treatment response, progression-free survival, (PFS) and overall survival (OS).

OUTCOMES OF INTEREST AND METHODS FOR ANALYSIS

The predominant method of assessing outcomes in oncology is time-to-event analysis, or survival analysis. Primary outcomes of interest are progressions-free survival and overall survival, the gold standard among oncology outcomes. Other outcomes requiring survival analysis are recurrence-free survival, distant metastases-free survival, and time to relapse. In each case, reporting the median and hazard ratios is recommended.

However, the potentially delayed response of immunotherapies results in an interruption in separation of survival curves between IO therapies and other treatments (eg, chemotherapy). This delayed separation violates an underlying assumption of a hazard function that is constant over time (ie, proportional hazards), resulting in a loss of power to detect differences between treatment cohorts [4]. Conventional analyses include non-parametric models (Kaplan-Meier curves, log-rank tests), but the potentially delayed response of IO therapies suggests that parametric models may be a better fit for analyses of IO therapy outcomes [2,5]. More flexible approaches like the exponential, Weibull, and piecewise exponential distributions capture the characteristic IO pattern of delayed treatment effects and, for a subset of patients, a plateau of long-term survival [2,5].

Other outcomes of interest in IO are immune response and treatment adherence. Adherence to IO drug is often observed through physician services (not pharmacy), because many IO drugs are infused at a physician's office or clinic. As is often the case with real-world data, sometimes the end dates of treatment are missing and must be imputed. For oncology drugs administered in cycles, these dates are estimated as follows: drug end date = drug start date + cycle length (in days) * # cycles.

Finally, when assessing outcomes in IO, it is important to control for supportive care services, especially when evaluating changes in patient quality of life. Supportive care services include nutrition therapy, naturopathic medicine, pain management, oncology rehabilitation, and mind-body medicine, among others. Capturing these data directly from patients allows for a 360-degree view of patient care and more informed analysis and interpretation.

The challenges to analysis of survival in IO therapies become more complex and dynamic when evaluating IO therapy alongside myriad potential combinations: chemotherapy, radiotherapy, molecularly targeted agents, vaccine therapies, other immunotherapies, other checkpoint inhibitors, and immune pathway agonists [6]. In addition to more flexible analytical approaches like exponential, Weibull, and piecewise exponential distributions, newer methods such as combined functions and spline-based models that fit piecewise polynomial functions to segmented portions of the data (non-separation, separation, plateau) further facilitate accurate assessment of outcomes in IO [6].

SUMMARY

We have seen a growing number of effective therapies since the first IO treatment was approved in 2010. The outlook is promising for cancer patients with a pipeline of breakthrough IO therapies from leading pharmaceutical and biotechnology companies. Deploying the right analytic approaches will strengthen the value of this research for healthcare decision makers and help to bring life-saving treatments to patients.

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Personalized Oncology Therapies Require Personalized Oncology Patient-Reported Outcome Measures

Jérémy Lambert, Mapi, Lyon, France

KEY POINTS

The treatment paradigm in oncology has shifted, moving from conventional chemotherapies to personalized medicine, including immunotherapies

Personalized medicine leads to individual-specific risks and benefits; thus patient-reported outcomes also need to be personalized to capture the relevant and appropriate concepts that matter to patients

Qualitative interviews with patients to collect their experience within an oncology trial: an innovative approach to document patient-perceived treatment benefit

Tumor size, overall survival, progression-free survival, treatment side effects, disease symptoms—these are all central clinical features to document in oncology clinical trials. While most features are assessed using imaging or biological samples, one should not forget the patient's voice to give a meaning to the observed changes on how a patient feels and functions. Only a patient can explain how a tumor shrinking by half its size actually benefits his daily life; only a patient can report how debilitating peripheral neuropathy can be; only a patient can report on how her pain or bowel movements have been affected by her treatment. The addition of the patient voice into the interpretation of the efficacy and safety data shall contribute to the assessment of the value of the treatment. This is particularly important in light of today's trend toward value-based healthcare defined by Porter as the system in which "achieving high value for patients must become the overarching goal of healthcare delivery, with value defined as the health outcomes achieved per dollar spent." [1,2]

> ...in the evolving era of cancer care, both a conservative approach with a legacy questionnaire and an innovative approach with specific questionnaires and qualitative interviews should be undertaken in immuno-oncology trials for the collection of patient-reported outcomes data

Collecting patient-reported outcomes (PRO) data has become a must in clinical research. Basch et al provided a comprehensive set of information on the selection, implementation, data analysis, and reporting of PRO in oncology trials [6]. PRO data are highly valued by major stakeholders, including payers and regulators. The European Medicines Agency (EMA) dedicated a specific appendix to PRO assessment in its guideline on the evaluation of anticancer medicinal products in man that came into effect as of November 2016. The US Food and Drug Administration (FDA) also refers to the use of PRO in particular to assess tumor symptoms and treatment-related toxicity in its 2007 guidance for industry on Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. The Agency is particularly interested in distinguishing through separate assessments, the treatment-related side effects, disease-related symptoms, and physical functioning [3]. More recently, the FDA confirmed its interest in having sponsors incorporating the patient perspective in oncology trials, in particular to inform safety profiles of the new cancer drugs under development [4]. The concomitant increase in the documentation of patient's perspective in oncology trials has been reported in the review by Zagadailov et al. Between 2006 and 2012 for about 85% of clinical oncology trials, sponsors disclosed on ClinicalTrials.gov the inclusion of a PRO to address an endpoint evaluating health-related quality of life and/or symptoms. In contrast, between 2002 and 2006 this percentage was down to 12% [5]. Cancer is by itself a group of myriad diseases with specificities and multiple treatment approaches, making it a challenging field for PRO assessments. Today, relatively few PRO questionnaires are used in oncology. The European Organization for Research and Treatment of Cancer Quality of Life (EORTC-QLQ) questionnaires and the Functional Assessment of Cancer (FACT) questionnaires have become standard instruments used in many trials for many types of cance, inccluding common cancers such as lung and breast cancers [6,7] as well as rarer cancers such as head and neck [8]. Their structures are very close, with a core module to which a specific cancer type module can be added. Their content is also quite similar, covering not only health-related quality of life, including physical functioning, but also treatment-related side effects and disease-related symptoms. >

A shift in treatment paradigm in oncology has occurred, leaving conventional chemotherapies and moving toward personalized medicine, with first the development of tumor-targeted therapies and more recently the development of immunotherapies such as the blocking antibodies to cytotoxic T lymphocyte antigen-4 (CTLA-4) and programmed death-1 (PD-1) [9]. With better efficacy and milder toxicity profiles of immunotherapy agents, the question around risk-benefit ratio has become less relevant, while the cost-effectiveness ratio and more particularly, the cost-utility ratio for such therapies have become a primary interest for health technology assessment bodies and payers.

There are limitations in the use of currently available questionnaires, in particular in light of the value-based healthcare, and authorities' requirements to use questionnaires for the purpose and context of use. These questionnaires have been designed for use in cancer patients with a range of disease stages and undergoing different treatments. Typically, these questionnaires have been developed initially to address the ethical question about the risk-benefit ratio of cytotoxic therapies. The frequency of administration of PROs was adapted to the treatment cycles. Thus, despite the fact that these questionnaires are validated and well-developed following standard methodology, they may become progressively outdated with the implementation of personalized medicine. Still, one should not totally move away from the standard questionnaires. While the shift in treatment paradigm is not completed, trials comparing conventional chemotherapies to immunotherapies would benefit from the use of the standard questionnaires to demonstrate patient-perceived treatment benefit of the new treatment in contrast to the former standard therapies.

For immunotherapies, the dose, treatment duration, and follow-up care are all patient-dependent parameters. Consequently, PRO also needs to be personalized to capture the relevant and appropriate concepts that matter to patients. In that sense, efforts are made by developing item banks to create customized questionnaires. This is the case of the EORTC item library, and also the National Institutes of Health-funded Patient-Reported Outcomes Measurement Information System (PROMIS®) and the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE™).

Still, there are several challenges in immuno-oncology trials. First, it is clear that there is a need to define specific hypotheses and use specific appropriate measures to monitor separately health-related quality of life, treatment-related side effects and disease-related symptoms. Very limited information is available in the literature to identify the concepts of interest to cancer patients receiving immunotherapies. Pre-established conceptual frameworks to support the the relevance of a concept or another is missing it, making it a challenge to define the right specific hypothesis and to choose the right PRO instrument that would document meaningful treatment benefits. A second challenge for the administration of PRO instruments resides in the sample size. Indeed, only patients with a specific genetic or epigenetic profile are eligible for specific immunotherapies. A third challenge in oncology trials is linked to cancers for which there are no currently available standard treatments. Such trials have frequently open-label, single-arm designs. In that context of multiple challenges, qualitative interviews with patients to collect their experiences with the study treatment within the trial may bring solutions to inform patient-perceived treatment benefit. Ideally, qualitative interviews should be integrated already in the first version of a study protocol from the start to maximize their added value to the trial. O'Cathain et al. described various contributions of qualitative research in clinical trials. It goes from the situation where the qualitative research is a stand-alone feature taking the advantage of accessing patients through the trial to the situation where the qualitative research is more than just complementary but informative and essential to the interpretation of the outcomes of the trial [10]. Integrating interviews at several time points of the trial to allow a longitudinal analysis should help capture changes over time linked to the study treatment as reported by the patients [11]. This approach requires on one hand the qualitative analysis to be performed continuously along the trial and on the other hand to develop continuously personalized follow-up interview guides to properly track the evolution of the concepts raised by an individual patient. While this could be cost- and time-consuming, this approach of repeated interviews within a trial limits the memory bias that could be an issue with exit interviews in lengthy oncology trials.

With better efficacy and milder toxicity profiles of immunotherapy agents, the question around risk-benefit ratio has become less relevant, while the cost-effectiveness ratio and more particularly, the cost-utility ratio for such therapies have become a primary interest for health technology assessment bodies and payers.

In conclusion, in the evolving era of cancer care, both a conservative approach with a legacy questionnaire and an innovative approach with specific questionnaires and qualitative interviews should be undertaken in immuno-oncology trials for the collection of PRO data. One should rely on the use of a standard legacy questionnaire to benchmark and compare to existing data. But, one should also use a specific outcome questionnaire for a specific hypothesis testing that could support a PRO claim in a drug label. Qualitative interviews should be implemented further to provide an explanation and understanding of the study treatment efficacy and safety, to guide the interpretation of the quantitative PRO and clinical data, and last but not least, to capture the individual features of personalized medicine. What indicates a statistically significant 10-point improvement on a 100-point scale assessing fatigue? Only patients can tell how it translates practically; it may not actually change anything in the patients' lives, but it could also lead to significant changes if they can visit their friends, go shopping, or prepare a meal without a required aid. This suggestion of adding

qualitative interviews fully aligns with the FDA public workshop that was held on December 18, 2017 on the collection and submission of patient experience data to inform medical product development and regulatory decision making.

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Estimating the Long-Term Outcomes Associated With Immuno-Oncology Therapies: Challenges and Approaches for Overall Survival Extrapolations

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KEY POINTS

Traditional parametric survival models are commonly used to estimate long-term survival in oncology health technology assessments, however, they cannot adequately represent complex hazard functions and may not be appropriate for modelling the underlying mechanism of action associated with immuno-oncology treatments.

Novel techniques for survival extrapolation, such as flexible parametric models, parametric mixture models and mixture cure models, and landmark-based response models can characterize complex hazard functions with turning points and changing slopes.

Cure, parametric mixture and landmark models may provide more insight into the potential mechanism of action of immuno-oncology therapies, compared with the more mechanistic traditional parametric survival models, or spline models.

TRADITIONAL SURVIVAL MODELING: LIMITATIONS FOR IMMUNO-ONCOLOGY

Cost-effectiveness analyses are key factors in reimbursement decisions made on new healthcare interventions around the world. Cancer treatments usually affect survival, and therefore cost-effectiveness analyses must estimate costs and benefits associated with competing treatment options over a lifetime period [1-4]. Trials have limited follow-up and in almost all instances, it is necessary to extrapolate beyond the trial data to estimate lifetime survival. Traditional parametric survival models are usually used for this task, whereby it is assumed that survival follows a particular underlying distribution. Different distributions can have a large impact on long-term survival estimates and although model choice is not straightforward, some guidance exists to help with this problem [5,6]. However, the extrapolation problem appears to be becoming more difficult—and even more important—with the development of immuno-oncology treatments, which have a number of unique characteristics, such as delayed effects, potential long-term survivors, and less mature survival data [7].

When treatments have delayed effects and long-term survivors, the implication is that the hazard function follows a more complex pattern than is modeled by the traditional parametric survival distributions. In the context of clinical trials of IO treatments in the metastatic cancer setting, the risk (or hazard) of death may be relatively low initially, due to trial inclusion criteria resulting in trial populations that are relatively fit compared to the more general disease population. However, given that trial participants have a severe disease, the hazard of death is likely to rise in the short-term. If treatment has a delayed effect, or only works for a proportion of subjects, the hazard may begin to fall, or at least its gradient may become less steep. In fact, in the longer term the situation may be even more complicated, as hazards may change again, increasing due to age-related mortality risks.

Traditional parametric models cannot adequately represent complex hazard functions with turning points. They also may be inadequate for representing underlying biomedical processes such as durable responses that have been observed for some IO treatments [8,9]. The models most commonly used in health technology assessment (HTA) are Weibull and exponential models [5,6]. Exponential models assume that the hazard remains constant across time, whilst Weibull models can represent hazards that either monotonically increase or monotonically decrease and nest the exponential as a special case. Other traditional models, such as Gompertz, log-logistic, log normal, and generalized Gamma models are either similarly restricted, or allow only a small amount of increased flexibility. Like Weibull models, Gompertz models can only represent hazards that increase or decrease monotonically but the rate of change has to be exponential. Log-logistic, log normal, and generalized Gamma models are able to represent hazards that initially increase and then decrease, but cannot characterize a second turning point or additional important changes in the slope of the hazard.

Therefore, if we believe that the hazard function associated with a new IO treatment (or any other treatment) is likely to have a turning point and/or important changes in slope over time, it is necessary to look beyond the standard parametric distributions when attempting to model long-term survival. Flexible parametric models [10,11], parametric mixture models and mixture cure models [12,13], and landmark-based response models [14] each provide a modelling approach that can characterize complex hazard functions with turning points and changing slopes. Each approach has strengths and weaknesses. There is little information in the literature regarding direct comparisons of these approaches; they have not been used largely in HTA decision making.

NOVEL TECHNIQUES FOR SURVIVAL MODELING: A CASE STUDY

In this case study, we introduced a comprehensive list of relevant methods for extrapolating overall survival (OS) data and illustrated their application to a clinical trial data set, the ATLANTIC study. We also compared and contrasted the model outcomes and provided insights on the tradeoffs in model selection in the context of the probable underlying biomedical processes for IO treatments. ATLANTIC is a phase II, open-label, single-arm trial of durvalumab in patients with stage IIIB–IV non-small cell lung cancer with World Health Organization performance status 0 or 1, who received at least 2 prior systemic treatment regimens, including 1 platinum-based. The trial results were presented at a plenary session entitled Immune Checkpoint Inhibitors in Advanced NSCLC at the World Conference on Lung Cancer [15].

We first fitted the OS data with the standard parametric models. Akaike information criterion and Bayesian information criterion suggested the log-normal as the best-fitting standard model to the trial data. Therefore, we selected the log-normal model as the benchmark against which to compare and evaluate different, more complex survival modeling approaches. We recognize that providing the best fit to the observed data does not mean that the log-normal model represents the best option for extrapolating beyond the trial period, but we decided to use it as a standard parametric model benchmark in order to avoid an unwieldy number of comparisons.

FLEXIBLE PARAMETRIC MODELS

Spline-based models [10,11] are flexible parametric models defined by piecewise polynomials. The point at which polynomials "join" are called knots. The modelled hazards are smoothed at the "knots" where the distributions change.

We considered that there were 2 key turning points in the observed hazard function of the data, and therefore 1-knot and 2-knot spline models were used to model the ATLANTIC OS data.

Although allowing more knots increases the flexibility of curve fitting, which often provides a better fit to observed data, it is important to select an approach that balances the flexibility in capturing the observed hazards and the risk of overfitting the data (eg, segmenting the data too thinly resulting in extrapolations based on a small amount of data). Indeed, fit to the observed data is often of secondary importance to the credibility of the extrapolated portion of the curve.

MIXTURE CURE MODELS

Mixture cure models were introduced more than 50 years ago [16]. They have been proposed recently to model survival of emerging cancer therapies, (eg, IO therapies) [13,17], as evidence has shown that these treatments may offer long-term survival ("cure") to certain patients in some indications. Mixture cure models can address the heterogeneity induced by the fraction of "cured" patients whose OS prognosis is assumed to be similar to that of the general population (depending upon how the "cure" is defined) instead of their counterparts who were not "cured."

The key assumption in this approach is the plausibility of a cure. Based on the assumption, the cure models estimate the percentage of patients who are cured and estimate the survival function for patients who are not cured. The risk of death of a cured patient is based on the background mortality of the general population.

We fitted the ATLANTIC OS data with a cure model and modeled this population as a mixture of cured and uncured patients, assuming a Weibull distribution for the survival of the uncured population. For background mortality, we used age- and gender-matched UK life tables based on data for the years 2012 to 2014.

Compared with the standard log-normal function, the mixture cure model predicts a much larger long-term survival rate and patient life expectancy.

> In the absence of long-term follow-up data, a scientifically grounded and consistent approach in survival extrapolations is desirable, and should serve as the foundation to demonstrate the potential value of immuno-oncology treatments.

PARAMETRIC MIXTURE MODELS

Parametric mixture models are a more general approach to address population heterogeneity. They can be used to model 2 (or more) distinct groups, without assuming a "cure." We used a mixture of 2 Weibull distributions, and the model estimated a probability for each patient of belonging to each group. On average, the probablity of belonging to group one (the first mixture) was 68%, and the probability of belonging to group 2 (the second mixture) was 32%, with group one being represented by a superior survival distribution.

RESPONSE-BASED LANDMARK MODELS

Based on the strong correlation between response and survival for IO therapies, response-based landmark models were considered as another approach to model the heterogeneity in overall survival in the ATLANTIC study.

These models distinguish "responders" from "non-responders" and model survival for each group separately. Response is declared, and subsequent survival is modeled, from a landmark point to avoid the bias that responders by definition have to survive to the point at which response is assessed. For the ATLANTIC study, we defined the landmark at 2 months, as the first tumor response assessment occurred at 8 weeks after treatment initiation in this trial. Response categories were defined as follows:

- Responder (R): Patients who remain progression free 2 months or more from start of treatment
- Non-responder (NR): Patients who progress or are censored prior to 2 months

Fifty-four percent of patients were categorized as responders and 46% as non-responders. The OS data after the landmark point show clear differentiation between the 2 response groups. Standard parametric models were fitted to each of the 2 groups, and the exponential distribution was selected for both groups as the best fit based on AIC and BIC, suggesting a constant hazard over time for each of the response categories. Visual inspection of both the survival function and the hazard function suggest that the landmark model provided a close fit to the observed data.

KEY LEARNING AND IMPLICATIONS

In this study, we explored a comprehensive list of alternative survival models using a data set from a recent IO clinical trial. All models provided a close fit to the observed OS data; however, their tails—the projections beyond the trial period—are very different [18]. Consequently, they estimate very different outcomes for mean OS, which is a measure of great importance used in cost-effectiveness models and health economic evaluation.

Therefore, validation of long-term survival projections is critical for choosing the "right" survival model. Relevant internal and external benchmarks should be cross-examined carefully and long-term clinical and real-world data should be identified and used to validate the survival extrapolations. At the same time, survival modeling should account for clinical rationale and validity. Among the models that were examined in this study, only the mixture model (mixture cure model as a special case, if a "cure" can be supported) and the landmark model offer potential insight into the biomedical mechanism of action. Nevertheless, in this application, these 2 approaches paint quite different pictures.

Although it is appealing to use a cure modeling approach to account for long-term survivors in cancer treatments, the validity of the assumed "cure" remains as the main challenge. The assumption of cure can only be verified with long-term follow-up data. However, for studies with limited follow-up, the key assumption cannot be validated. In addition, the estimate of the cure fraction could be sensitive to the choice of parametric distribution. Therefore, cure models could generate misleading results.

Parametric mixture models can be used to model distinct survival distributions within data when a cure is not supported. These provide great flexibility in the shape of hazard and survival functions, although the flexibility of the modeling approach may lead to a high level of uncertainty in parameter estimates.

Response-based landmark models acknowledge the distinction between responders and non-responders and have a strong clinical rationale, provided the response measure is prognostic. It is therefore important to demonstrate that the chosen response measure is a reliable surrogate for survival. In addition, the model can be sensitive to the choice of the landmark time-point. The landmark should be selected such that it minimizes the loss of patients who die prior to the landmark, and accounts for vast majority of responders. In our case study, a key finding was that the OS projection for responders was the key driver of uncertainty, because the patients who were still alive at the end of trial follow-up period were mostly responders.

In general terms, we prefer the cure, parametric mixture, and landmark models in that they provide more insight into the potential mechanism of action of IO therapies than the more mechanistic traditional parametric survival models, or spline models. Nevertheless, due to the limited follow-up in the current ATLANTIC trial, more data are required to provide a definitive choice as to which model offers the best fit and the most appropriate option for extrapolation.

We are still at an early stage in the development of IO therapies. For many indications and many therapies, the mechanism of action is yet to be fully understood and the long-term survival trend of patients is yet to be observed. This adds to the challenge of modeling long-term survival in IO. It also highlights the importance of advancing the basic scientific understanding on the mechanism of action and collecting long-term outcome data from clinical trial studies and real-world evidence studies. In the absence of long-term follow-up data, a scientifically grounded and consistent approach in survival extrapolations is desirable, and should serve as the foundation to demonstrate the potential value of IO treatments.

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Additional information:

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Developing and Paying for Gene Therapies – Can We Resolve the Conflicts?

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KEY POINTS

A one-time treatment that yields a cure for a rare and devastating condition is likely to command a high price, which sets up conflicts between innovators and payers.

The evidence packages supporting gene therapies often include short-term data from small trials that may employ atypical study designs, and this makes it difficult to assess the value of gene therapies using typical appraisal methods.

To navigate the conflicts and find mutually agreeable solutions, innovators and payers must collaborate with multiple stakeholders including patients (and their families), providers, and policy makers.

Gene therapies recently have become available in Europe, and they will soon be available in the United States. Gene therapies may bring within reach the possibility of one-time treatments that yield benefits of a long period of time, perhaps even a lifetime. However, such sophisticated technology comes at a cost; some analysts are anticipating prices of $500,000 to $1 million per treatment, and this raises questions about affordability [1]. Recent experiences with drugs to treat hepatitis C, another curative therapy that strained the resources of the healthcare system, are still fresh in the minds of payers and policy makers thus tempering their enthusiasm for gene therapies. In this article, we take a multi-stakeholder view of gene therapy in the hopes of illuminating the key issues and fostering continued dialogue to find the right way to integrate these treatments into the healthcare system.

GENE THERAPY

According to the US Food and Drug Administration (FDA), gene therapies are *"products that mediate their effects by transcription and/or translation of transferred genetic material and/or by integrating into the host genome and that are administered as nucleic acids, viruses, or genetically engineered microorganisms. The products may be used to modify cells in vivo or transferred to cells ex vivo prior to administration to the recipient. [2]"* Once thought to be futuristic, gene therapies are rapidly becoming a reality. A recent evaluation of gene therapies in late-stage clinical development indicated that 23 gene therapies are in phase III clinical trials and the therapeutic areas with the largest number of products are cancer and rare diseases [3]. The FDA's Commissioner Scott Gottlieb recently acknowledged the coming wave of gene therapies and plans to issue a "suite of disease-specific guidance documents" on gene therapy products in 2018. The documents will describe a modern approach to the evaluation of gene therapies for high priority conditions, new clinical measures or endpoints, and provide advice for industry on development pathways [4]. This is likely to shape evidence development and value assessment in a significant way and bears watching by all parties involved. Further heightening the interest in this area is the fact that Luxturna™ (voretigene neparvovec-rzyl), a gene therapy for inherited retinal blindness due to mutations in the RPE65 gene, was approved by the FDA on December 19, 2017 [5]. With these types of treatments now within sight, it is important to start thinking about the issues raised by gene therapies because they will create conflicts between manufacturers and payers, and how those conflicts are resolved will have ramifications for patient access. **Table 1** lists a few of the conflicts, and these will be explored in greater detail as they are likely to shape the scientific, economic, and policy discussions to come. >

Table 1: Conflicts for innovators and payers created by gene therapies

Innovator Challenge	Payer Challenge
Innovators seek fair compensation corresponding with the level of risk required to develop gene therapies	Concerns about affordability and fear of bankrupting the healthcare system
Safety and efficacy are supported by relatively short-term data	Concerns about the certainty of safety and durability or response (Is it truly a cure?)
Developing gene therapies for rare conditions requires trials that utilize small sample sizes, single-arm trials, novel trial designs, and surrogate endpoints	Payers want robust evidence to inform decision making

AN INNOVATOR'S PERSPECTIVE

Gene therapies are distinctly different than traditional drugs and biologics but they share many similarities, too. Like traditional pharmaceuticals, a gene therapy must address an unmet clinical need and must demonstrate that it is safe and effective for the intended indication to earn FDA approval. Once it is approved, payers will use their usual technology assessment approach, at least initially, to evaluate the overall value of a gene therapy. With this approach, the standard of care is still the most relevant comparator for a gene therapy. Some argue that the same standard metrics (eg, incremental cost-effectiveness ratio) can be used to measure the value of a gene therapy, but the process will include more unknowns. Unlike most traditional pharmaceuticals, gene therapies offer the potential for a one-time treatment that produces long-term, possibly even lifetime, benefits. Traditional pharmaceuticals are often used on a chronic basis or for acute treatments. Assessing the value of a lifetime benefit may be difficult to capture. Gene therapies often target rare diseases with known genetic defects and because of the very small patient populations involved, the supporting evidence is often derived from small clinical studies with single-arm, unblinded trial designs. The high cost of developing a gene therapy combined with the small patient population in which to market it means the short-term cost-per-patient is expected to be higher than for traditional pharmaceuticals. Additionally, gene therapies may require complex procedures that blur the line between a "product" and a "process." For example, chimeric antigen receptor T-cell (CAR-T) therapies utilize a manufacturing process that involves collecting cells from the patient, ex vivo modification to target certain cancer markers, and then reinfusion back into the patient where they exert their therapeutic actions.

> ...it is important to start thinking about the issues raised by gene therapies because they will create conflicts between manufacturers and payers, and how those conflicts are resolved will have ramifications for patient access

Gene therapy innovators need to think beyond regulatory approval and must consider how they will demonstrate the commercial value of their product to payers to secure reimbursement in the marketplace. Innovators will need to collect relevant comparator data to build a convincing argument that the new therapy provides an important advance over existing therapies. A limited data set at launch raises questions about the certainty of effect in the real world. Studies lasting 2 to 3 years, although potentially sufficient for regulatory decisions, are still relatively short for a treatment that proposes to have a lifelong benefit. This raises questions about durability of response as well as the long-term safety profile. To this end, real-world evidence may play an important role in augmenting the evidence gained by clinical trials, address the questions of certainty and durability, and help establish the value of gene therapies. To navigate these challenges, manufacturers will need to work closely with multiple stakeholders, including payers, patients (and their families), providers, policy makers, and investors. As a reward for undertaking these challenges, innovators want to be fairly compensated for their innovations and risks; without adequate compensation, future gene therapies may not be viewed as commercially viable thus discouraging the financial investment needed to bring future gene therapies to market.

A PAYER'S PERSPECTIVE

While the potential of gene therapy is exciting, payers have concerns about how to fit this new technology into a healthcare system that already struggles to meet the needs its members. Some think gene therapy will be too expensive for the system to absorb, especially if multiple products come to market. With prices of $500,000 to $1 million per treatment, there is fear that gene therapies will bankrupt the system. This raises several questions for manufacturers, payers, and society. Does the new therapy actually meet the unmet needs of the condition being treated? Sometimes the outcomes used to gain regulatory approval (eg, the 6-minute walk test) do not reflect the types of things that are important to patients, such as increased quality of life. Payers will want to see improvements in other outcomes like productivity and reduced care burden. Is the effect truly a breakthrough, or is it merely a small incremental improvement over existing therapies? Even if the gene therapy addresses the unmet need, is the manufacturer entitled to the full "value" of the gene therapy and all the costs it may potentially avoid? Many treatments are not priced to capture fully all the potential cost offsets associated with them; two examples include vaccines and appendectomy procedures. What if the treatment effect wears off? Will a second treatment be needed? In addition, what if a patient dies early and none of the promised cost savings is realized? These are some of the questions with which payers are starting to wrestle.

Financing gene therapy will also be a challenge. The US healthcare system is not constructed to handle payment for one-time cures easily, especially when members move among health plans. Typical negotiations about price between payers and manufacturers can address cost concerns to a certain degree but additional approaches will be needed. Given the high upfront costs of gene therapy, some mechanism for spreading payments over time will be desired, either through amortization or manufacturer-based financing options. Risk-sharing agreements may also be a path forward, where outcomes are tied to reimbursement and if a patient fails to respond or the condition relapses, they stop paying.

Payers also worry about having the necessary clinical evidence upon which to make decisions. Due to the ethical constraints associated with studying gene therapies, clinical trials often utilize small populations, study surrogate endpoints, employ non-standard trial designs, and have only short-term follow-up periods. This can lead to optimistic estimates of the expected outcomes. Some of these therapies will require a procedure to deliver it and a sham procedure arm may be unethical to employ as a comparator arm. The lack of long-term evidence, although not unique to gene therapy, makes it difficult to evaluate the evidence critically and to gauge the risk-benefit profile associated with gene therapy.

Collaboration and dialogue will be crucial for securing access. Manufacturers should engage in early discussion with payers to incorporate the appropriate health economic outcomes research (HEOR) perspectives, relevant outcomes, and data that payers

need to support coverage criteria and policy development. Providers may need education about the disease and gene therapy, as well as other issues surrounding the evidence and reimbursement challenges, especially providers bearing risk though accountable care organization models. Patients will need to understand the risks associated with treatment and how their desired outcomes match up with the outcomes expected from treatment. Finally, plan sponsors will be asking, "What am I getting for all this money?" A clear answer will be needed to facilitate discussions about access.

A EUROPEAN PERSPECTIVE

In the European Union, gene therapies fall under the broader category of "regenerative medicines" and eight such products have been approved to date. Three of the products can be considered gene therapies: Glybera® (alipogene tiparvovec), Strimvelis™ (autologous CD34+ cells transduced to express ADA), and Imlygic™ (talimogene laherparepvec), although some do not consider Imlygic to be a true gene therapy. The European Medicines Agency's Priority Medicines pathway, like the FDA's Breakthrough Therapy designation, provides for enhanced support for medicines that target an unmet need and roughly one third of PRIME-designated drugs are gene therapies [6,7]. While the drug development pipeline appears to be rich with gene therapies, reimbursement for marketed products remains a challenge. For example, Glybera did not achieve reimbursement approval, was used in only a single patient, and is now being withdrawn from the market. Other regenerative medicines also have experienced similar challenges including market withdrawal. However, one therapy is taking a different approach. Strimvelis, a gene therapy for severe combined immunodeficiency, was approved by the Italian Medicines Agency and is being reimbursed under a money-back guarantee agreement with the manufacturer: if the drug does not work, the company will return the money. [8] Strimvelis is currently undergoing evaluation via the National Institute for Health and Care Excellence (NICE) Highly Specialized Technology review process; a draft guidance in October 2017 recommending Strimvelis when no suitable stem cell donor is available, and a final decision is expected in early 2018 [9]. However, it remains to be seen if similar reimbursement agreements will be reached in the United Kingdom or other countries.

One question that remains unanswered is what is the best way for health technology assessment organizations to assess gene therapies? To answer this question, NICE recently set out to explore whether its existing methods and processes were appropriate for the assessment of regenerative medicines. It commissioned a mock technology appraisal using a hypothetical product: a CAR-T therapy used for the treatment of relapsed or refractory B-cell acute lymphoblastic leukemia [10]. Incremental costs, quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratios (ICERs) were calculated in the typical fashion. In the base case, the ICER was above the £50,000 willingness-to-pay threshold, it had the lowest probability of being cost effective, and thus was not recommended. However, in the most favorable scenario, a product discount was applied to the base-case price and combined with lifetime leasing arrangement (ie, payments are stopped if the patient dies) and this approach resulted in an ICER below £50,000, a higher probability of being cost effective, and a recommendation in favor of reimbursement. The analysis found that the existing NICE appraisal methods and decision framework could be applicable to regenerative medicines. However, not all agree with the findings because the hypothetical product selected for the mock appraisal was designed to fit the existing approach. The existing framework could work, but it may not be the most suitable method to assess a regenerative medicine. Still, the exercise demonstrated the importance of innovative models that could resolve uncertainty and address budget impact issues stemming from high upfront costs, although it seems that more work needs to be done [11].

ICER POLICY SUMMIT ON GENE THERAPY

As the United States prepares for the introduction of gene therapies, many questions remain about the best method for assessing and paying for them. The Institute for Clinical and Economic Review, a US-based independent nonprofit research institute, convened a policy summit in December 2016 to analyze the clinical potential of gene therapy and the unique challenges in developing and evaluating evidence on their effectiveness and value. The summit was attended by 33 healthcare leaders from 20 payer and life science companies that make up their membership group. The major themes that arose from the discussions echo the perspectives described above and included concerns about generating the evidence necessary for decision making, uncertainty of the durability of effect and safety, and affordability. A white paper on the summit, available for download, describes the issues in detail and provides policy recommendations for both payers and manufacturers [12,13].

CONCLUSIONS

Gene therapies are coming to the United States soon so more work needs to be done to sort out the sources of conflict between innovators and payers. Whether we can resolve the conflicts described above remains to be seen, but the path forward appears to involve collaboration among multiple stakeholders. If we cannot resolve these conflicts, then our healthcare system—and society—run the risk of missing the benefits of gene therapies. Is that really the outcome we want?

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Additional information:

The preceding article was based on a workshop presentation presented at the ISPOR 22nd Annual International Meeting. To view this presentation, go to https://www.ispor.org/Event/ReleasedPresentations/2017Boston#issuepanelpresentations

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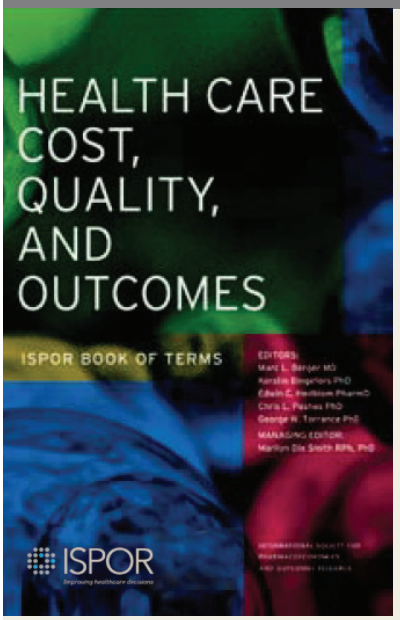

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Q&A

Discrete Choice Experiment Methods: An Interview with F. Reed Johnson, PhD

Our editorial board member for *Value & Outcomes Spotlight* was fortunate to sit down with F. Reed Johnson, PhD, Senior Research Scholar at Duke University's Clinical Research Institute, to discuss patient-reported outcomes and discrete choice experiment methods. His current research involves quantifying patients' willingness to accept side effect risks in return for therapeutic benefits and estimating general time equivalences among health states. He led the first FDA sponsored study on patients' willingness to accept benefit-risk tradeoffs for new health technologies. The study was used to develop recent FDA guidance on submitting patient-preference data to support regulatory reviews of medical devices.

Value & Outcomes Spotlight: You are recognized as a leader in patient-reported outcomes (PROs) and especially in discrete choice experiment (DCE) methods. Could you describe the advantages and more common applications of DCE in health technology assessment (HTA)?

F. Reed Johnson: Choice experiments simulate decisions requiring respondents to evaluate a series of 2 or more experimentally constructed health interventions, health states, or health policies. The preference elicitation typically is a response to the question: "If these were the only alternatives available, which would you choose?" Under appropriate experimental controls and using appropriate statistical analysis, the pattern of such choices reveals respondents' implicit relative-importance weights for the features used to describe the constructs of interest.

There is persistent confusion about the relationship between PROs and choice experiments. This confusion arises because both PROs and choice experiments obtain data by direct elicitation from individual patients. In fact, the 2 kinds of data share no common conceptual framework or intellectual history. Choice experiments do not collect outcomes data and PROs are not experiments.

If HTA is narrowly defined as cost-effectiveness analysis, choice experiments currently are not commonly used for such purpose. However, researchers are beginning to demonstrate use of choice-experiment data to quantify generalized healthy-time equivalents and to obtain patient-centric weights for aggregating items in value frameworks. Defining HTA more broadly as the systematic evaluation of health technology to inform decision making, choice experiments can be useful in all stages of the product life cycle, including prioritization in early product development, clinical-trial design, weighting clinical-trial data to obtain patient-relevant composite endpoints, regulatory benefit-risk assessments, value frameworks for market access, evidence reviews for clinical guidance, and shared decision making.

Do you consider DCE useful to be used in combination with multiple criteria decision analysis (MDCA) tools?

There also is persistent confusion about the relationship between MCDA and choice experiments. MCDA as typically implemented is a process to promote consensus and transparency in small-group decision making. Choice-experiment evidence could appropriately be included along with clinical-trial evidence and other considerations in supporting such deliberations.

How is the process of choosing and building of attributes and levels conducted? Is it essential to involve patients in that step? How much time and effort should be dedicated to this part of DCE?

Poor attribute identification and definition is the primary cause of limited relevance and high measurement error in DCE studies. Attributes and levels are defined using either top-down or bottom-up approaches, depending on the purpose of the study. If the study is intended to provide weights for trial-data composite endpoints or for benefit-risk assessments, then the attributes and levels must map directly to the trial endpoints to be evaluated. If the study is intended to identify and quantify outcomes and processes most salient to patients, then attributes and levels are obtained through a combination of existing evidence, clinical experience, and most critically, direct patient engagement.

There is no established good-practice guidance for engaging patients in identifying salient attributes. Implementation can range from informal conversations with patients to a formal sub-study to prioritize a list of possible attributes. Many researchers advocate use of focus groups. Approaches can include direct ranking, card sorting, best-worst scaling, or Likert-scale exercises. Attributes and levels commonly are verified in face-to-face interviews used to evaluate draft instruments. Necessary effort to identify, define, and test attributes in survey development sometimes can require half of the resources available for a study.

Do you see, in a near future, DCE replacing traditional instruments for valuing technologies or as a tool for eliciting utilities?

I have been expecting that to happen in the "near future" for 20 years! As a young environmental economist in the 1980s, I saw stated-preference methods based on standard economic utility theory integrated into formal technology assessments in every area of applied economics requiring nonmarket valuation except health. There seemed to be no logical basis to treat health investments differently than investments in transportation, food safety, water management, pollution control (with health as the most significant benefit category), habitat protection, or homeland security. However, traditional HTA approaches have continued to enjoy widespread acceptance and enormous inertia. Recent emphasis on patient-centric healthcare, value frameworks, FDA guidance on submitting patient-preference data to support regulatory benefit-risk assessments, and studies to obtain DCE-based tariffs for EQ-5D health states finally indicate a significant sea change. I am hopeful that it will not take another 20 years before choice-experiment methods routinely are taught and used for valuing health technologies.

Acknowledgement

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